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Paediatric Intensive Care in Sweden

An epidemiological survey focusing on Diagnostic Panorama, Outcome and Factors influencing Long-term Mortality

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Till de tre kvinnorna i mitt liv Emma, Hanna o Lipika.
Ni gör det mödan värt!

Och mina fantastiska vänner, nu blir det äntligen kalas!

PROLOGUE

ABSTRACT

Background

In the 1990´s, studies of paediatric intensive care around the world had shown better outcome for children treated in PICUs compared to adult ICUs (AICU). In Sweden no nationwide data on children needing ICU care was present.

Aim/Methods

To quantify the Swedish need for and outcome of intensive care for children, a retrospective multicenter cohort study was set up to include all children admitted to intensive care in from March 1998 to March 2001. The cohort was monitored for five years and survival data analyzed. (**Study I**). When analyzing the data, it was obvious that PIM2 score and a more extended data set to study factors involved in long-term mortality post PICU care was needed. A new three-year cohort was formed, this time with only PICU admissions from January 1, 2008 to December 31, 2010 (**Study II***)*. During the time of the study PIM2 score was not reported from AICUs.

Arterial blood gas (ABG) is one among several variables included into the PIM2 score. We felt that to minimize unnecessary trauma, the routine use of ABG was unwarranted unless clinically indicated or for certain groups of children. We therefore studied a subset of the cohort to determine how PIM2 score predictability was influenced with or without ABG (**Study III**).

It was noted that some of the children who died in the years after discharge, did so outside the PICU (**Study II**). We therefore performed an additional study of the 268 children whom died in the latter cohort to determine if limitation of medical treatment (LOMT) was the factor opposing PICU readmission for these children when turning fatally ill (**Study IV**).

Results/Conclusions

We found that the outcome of intensive care for Swedish children was on par with international published data and 56% of the paediatric intensive care admissions were to AICUs. A 20-fold increased risk of death five years post PICU discharge was also found for the cohort (**Study I**). In the following cohort we found that having multiple admission (MADM) compared to single admissions (SADM) and/or a complex chronic conditions (CCC) significantly impaired the long-term outcome for five out of the seven different admission diagnosis groups (**Study II**). We also found that since **Study I** there was an increase in transfer from AICU to PICU from 65 to at least 278 children. In **Study III** we could show that the PIM2 score only becomes more accurate (although not significantly) if ABG is taken for the admission diagnostic group respiratory. In **Study IV** we in detail studied the 268 children that died in the cohort and could show that 123 (46%) died outside PICU. At the time of death 75% of them had a LOMT in place limiting readmission to PICU. Of the children not readmitted to PICU, 75% also had a CCC and 60% were males.

LIST OF PUBLICATIONS

I **Immediate and 5-year cumulative outcome after paediatric intensive care in Sweden**
Gullberg N, Kalzén H, Luhr O, Göthberg S, Winsö O, Markström A, et al:
Acta Anaesthesiol Scand. 2008; 52:1086–1095. https://doi.org/10.1111/j.1399-6576.2008.01711.x PMID: 188401

II **Survival after PICU admission: The impact of multiple admissions and complex chronic conditions**
Kalzen, Hakan; Larsson, Björn A ; Eksborg, Staffan ; Lindberg, Lars ; Edberg, Karl Erik ; Frostell, Claes.
PLoS ONE, April 5, 2018, Vol.13(4)

III **To have or not to have an arterial blood gas sample for PIM2 estimation Can unnecessary harm be avoided in acutely ill children?**
Håkan Kalzén, Tova Hannegård Hamrin, Lars Lindberg, Ola Ingemanson, Peter Radell, Staffan Eksborg
Acta Paediatrica DOI:10.1111/apa.14580. e-published September 16, 2018

IV **Mortality after PICU care. Diagnostic panorama, place of death and impact of Limitation Of Medical Treatment (LOMT)**
H Kalzén, BA Larsson, L Lindberg, O Ingemansson, C Frostell, S Eksborg
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ABG	arterial blood gas
ANZPIC	Australian and New Zealand Paediatric Intensive Care registry
CVS	cardiovascular
ECMO	extra corporeal membrane oxygenation
EMA	European Medicines Agency
FiO2	fraction of inspired oxygen
GI	gastrointestinal
Inj	injury
IQR	inter quartile range
KM	Kaplan-Meier
LIVA	long term paediatric intensive care unit
LOMT	limitation of medical treatment
MADM	multiple admissions
Misc	miscellaneous
MPE	mean prediction error
MR	mortality rate
MRR	mortality rate ratio
PaO2	arterial oxygen tension
PDR	predicted death rate
PICU	paediatric intensive care unit
PIM	paediatric index of mortality
Post Op	postoperative
Resp	respiratory
RMSE	root mean square prediction error
rs	Spearman rank correlation coefficient
SADM	single admissions
SFBABI	Svensk förening för barnanestesi och barnintensivvård
SMR	standardized mortality ratio
SPOR	Svenskt Perioperativt Register
TBOT	the bloody obvious test

1 INTRODUCTION

At the out start of this thesis Sweden had three dedicated PICUs. Paediatric surgery and medicine were thought to have good outcome in par with the rest of the world. However national outcome data regarding PICU care and figures on demand of intensive care for children in Sweden was scarce. North America, Europe and Australia called for centralization of PICU care but the overall situation in Swedish was unknown.

The tabloid medical perspective

September 13, 1961 the Swedish tabloid "Expressen" reported on the 6th English paediatric surgeons congress in Stockholm. The Swedish surgeons and anesthetists had been very progressive and as an homage the British congress was placed in Sweden. The Swedish anesthetists presented their progressive view on ventilating the newborn infants, but the British surgeons were sceptic. At the same time a machine for mechanical ventilation was just being finished at the Great Ormond Street children's hospital for perioperative "artificial ventilation". This novel approach of mechanical ventilation was suddenly put in a very dramatic context when the Swedish anaesthetist, Hans Feychting urgently needed to leave the congress and run to Kronprinsessan Lovisas hospital, the Paediatric hospital where he was running a newly opened PICU.

At the hospita, with mechanical ventilation, he had to assist a newborn. The British surgeons tag along (and a TV team from Swedish news "Aktuellt") and watch as a 1700g child was being ventilated and treated for "hyaline membrane disease".

The Engström ventilator, Kronprinsessan Lovisas Hospital.

In those days just ventilating a sick child was considered as a very advanced and spectacular medical treatment. Subsequently the whole incident made the headlines of the tabloid press. Unfortunately, the child eventually died, which of course also was reported in "Expressen".

Rapid intensive care development

After the second world war the surgical, technical and anaesthesia development had been rapid and there was an increasing demand for care of patients in the perioperative period as well as during the outbreaks of polio.

The Danish anesthesiologist Björn Ibsen organized the care of ventilated polio patients during the ongoing polio epidemic in Copenhagen. He is often considered to be the father of modern intensive care since he started to ventilate the patients with positive pressure using a tracheostomy instead of employing a negative pressure of an 'iron-lung'.[1,2] Ibsen set up his ICU in 1953. He was managing the polio outbreak in Denmark at the same time as Sweden's first ICU was formed in Borås 1952 by Åke Bauer who made an immense

pioneering effort.[3] He held a speech during the Swedish anesthetists yearly meeting in Borås 1953 with the title; "One year's experience of postoperative- and Intensive care". Scandinavian anaesthetists had been very early in adapting the concept of centralizing the sickest patients and the network of the Scandinavian Society of Anesthesiologists played an important role in the sharing of new technology and experience of different treatments.

The intensive care of children

Medical developments starting in the 1920´s with specific focus on artificial ventilation, thermoregulation and feeding eventually led to the development of neonatal intensive care units (NICU) with focus on the premature babies.[4] The first PICUs cared for all children that were severely sick and specifically needed ventilation, from premature babies to post-operative care of adolescents. Although there still can be some overlap found, the NICUs and PICUs are now very different entities.

The first PICU in the world was set up in Gothenburg 1955 by Dr Göran Haglund and the experiences of the first 300 days were reported in Helsinki at the 4th congress of the Scandinavian Society of Anesthesiologists.[5] Swedish anesthetists were pushing the envelope for different treatments and in 1958 Haglund published the first case report on successful mechanical ventilation of a patient with the so called IRDS/hyaline membrane disease.[6] Like many anaesthetist at that time Göran Haglund, Åke Bauer and Bjørn Aage Ibsen were all trained in the US and had been influenced by the ideas that specialized units for the sickest patients was the future. Inspired by his colleagues, in 1961 Hans Feychting started the second Paediatric Intensive care unit in the world at Kronprinsessan Lovisas hospital. The PICU at Kronprinsessan Lovisas hospital was simply called the emergency ward, "akutavdelningen".

In the following decade ICUs and PICUs were organized in Europe, Australia and north America[7-9] and a remarkable development of intensive care was to follow.

2 BACKGROUND

Differences in paediatric and adult physiology and reason for ICU admission

Adult and paediatric physiology differs in many important aspects. Due to the much smaller diameter of the bronchial tree, airway resistance obviously can be very high in the newborns compared to adults.[10] The undeveloped diaphragm and a less rigid thorax composition also leaves the newborn vulnerable to ventilatory challenges.[11] Oxygen consumption per kg bodyweight is significantly higher and circulatory physiology is different than adults[12-15] The cause of ICU admission is also different for children and adults. In Sweden cardiovascular disease in the most common reason for PICU admission whereas injury is the most common in children admitted to AICUs.[16] The adult ICU-patients have a diagnostic panorama dominated by the influence of the ageing physiology, especially the circulation, and infections[17] Specialized units with specific knowledge of paediatric circumstances was apparently necessary to improve quality of care for the newborns and children.

Artificial ventilation

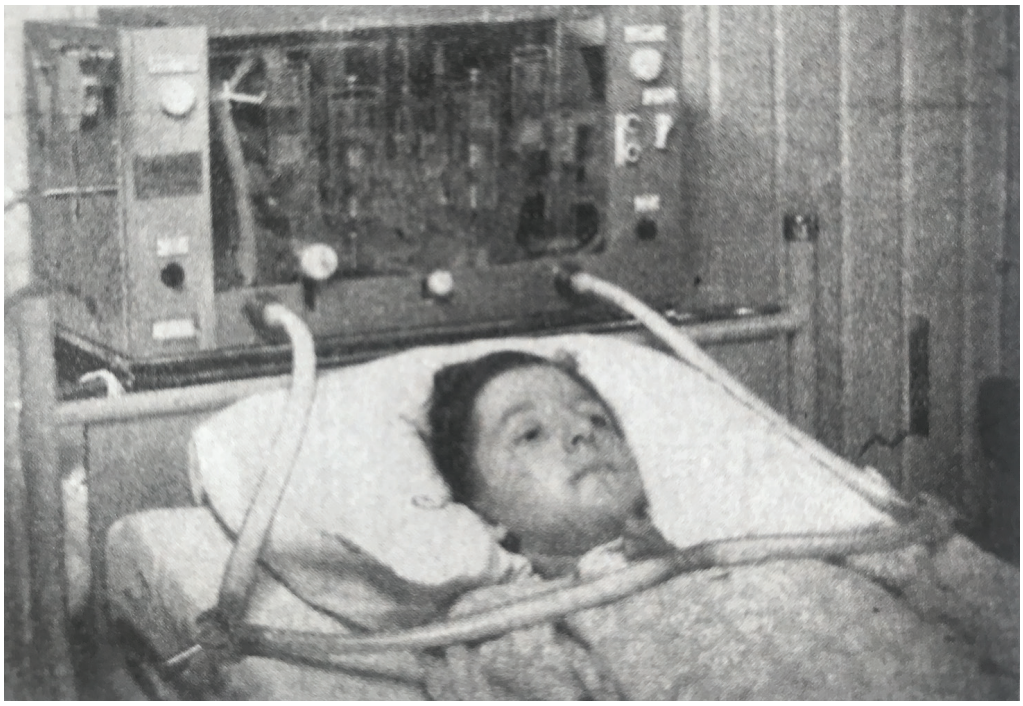
The concept of positive pressure ventilation with the use of a tracheostomy was first published in 1543 by Andreas Vesalius.[18] To quote: "But that life may be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air".

This was then forgotten until Galen further explored the interaction between ventilation and circulation.[19] The anaesthesia of patients that needed surgery have come in different pharmacological ways since first described in China in the Book of Master Han Fei (c. 250 BC).[20] Patients needed to relay on spontaneous breathing to survive and the concept of a controlled airway during Anaesthesia was first reported in 1871 by German surgeon Friedrich Trendelenburg[21-24] who used tracheostomy for general Anaesthesia. The alternative way through orotracheal intubation was reported in 1880 by Scottish surgeon William Macewen[25-27] The intubation procedure as a reliable alternative for controlling the airway during surgery was finally reported in 1913 by Chevalier Jackson.[28] He introduced a new concept with a light-source at the distal tip of a new long blade and made it possible to intubate safely. In 1913, Henry H. Janeway put a batteries in the handle, made a central notch in the blade and put a slight curved tip on the blade.[29] These improvements made the intubation technique very popular and together with trache-

ostomy and a development from steel cannulas to plastic and silicone tubes, eventually patients could be positive pressure ventilated longer and treated for in the intensive care setting.

In the late 19´century the negative pressure ventilators, so called iron lungs were developed. They caused a lot of practical problems since the patients were enclosed and the gas exchange was sub-optimal. The Polio epidemics of the 1950´s with a high demand for ventilators made the ventilator market soar. In the beginning these new ventilators were not adapted to the paediatric patient and adjustments had to be made.

A typical sign of the times was when Dr Göran Haglund and his colleague Åke Waldinger, now with a lot of experience from ventilating polio-patients in Gothenburg, became two among many pioneers who tried to find ways to improve the ventilatory care in children. They developed the Gothia ventilator 1954 and presented it in the mid 50´s.[30] It was still running at least 20 years later.[31] Gothia was very advanced with humidified and filtered air, it could be hand-cranked and if the gas supply stopped, room air could be used. It could be place at the end of the patient bed and transporting the patient was possible.



The Gothia ventilator by Göran Haglund and Åke Waldinger: Nordisk Medicin 1955: 53: 804

Another example of how physicians tried to share knowledge is the published recipe on how the Siemens 900b ventilator could be tweaked with some new parts (and sometimes duck-tape) to achieve a machine suitable for ventilation of newborn infants.[32]

The sharing of medical development and experience at the beginning of the 50´s were mainly through the network of Scandinavian Society of Anesthesiologists and the

yearly rapport called the "proceedings of the yearly congress" published the latest news. The scientific paper Acta Anaesthesiologica Scandinavica was established in 1957 and is the official publication of the now called Scandinavian Society of Anaesthesiology and Intensive Care.

Outcome

There are some published and anecdotal data on outcome for subgroups of paediatric patients in need of PICU care from the -50´s and -60´s. For example, before 1952 ventilated polio patients had a three-week polio respiratory mortality above 80% in Scandinavia. It dropped to 40% in Copenhagen 1952 and 30% in Stockholm 1953. From 1956 to 1961 there were no deaths within two years after PICU care reported among patients with polio that needed ventilator treatment.[33] Parallel to progress of ventilatory treatment and outcome there were some reports on children with sepsis and septic shock. Mortality reported from Minnesota Medical center between 1958 and 1966 for children <16 y of age with gram-negative sepsis, was 60% for medical patients and 40% for surgical categories.[34] For septic children with septic shock the mortality rate was 98%! Since then the mortality rate have decreased dramatically thanks to modern intensive care.[35]

In order to measure and compare outcome, the need for a systematic approach was obvious and the first published attempt to use as scoring system to evaluate PICU mortality was published in 1982, the therapeutic intervention scoring system (TISS).[36] TISS was used to evaluate the outcome of 461 North American PICU patients. The mortality rate was 18%, dominated by admission diagnosis trauma 29%, cardiac 25% and malignancy 22%. Sepsis only had 6% mortality rate, but then again diagnostic grouping was defined as "population characteristics" and still needed some attention to be comparable between cohorts. In this study the TISS score could not differentiate between survivors and non-survivors. Additional studies with TISS and the Clinical Classifications System (CCS) could demonstrate an association with outcome. Higher scores were associated with higher mortality risk.[37]

Pediatric Risk of Mortality Score, PRISM

In North America the TISS, CCS and eventually the developed Physiology Stability Index (PSI) were adopted in the evaluation of the PICU population.[38,39] The PSI assessed 34 variables from seven organ systems, with scoring regarding the degree of abnormality. PSI was further developed into PRISM and PRISM III with 17 variables (published in 1996) that became a well-established standard mortality prediction model for PICU care,[40,41] The same cohort of 11,165 children used for PRISM III was later utilized to develop the Pediatric risk of mortality III-Acute Physiology Score (PRISM III-APS).[42] PRISM III-APS then contained 21 physiological variables that better could detect smaller changes in physiologic status. Since the PRISM was based on the most abnormal physiologic values during the first 24h, a poor initial PICU treatment would have high scores as a result. A worse outcome for a unit with

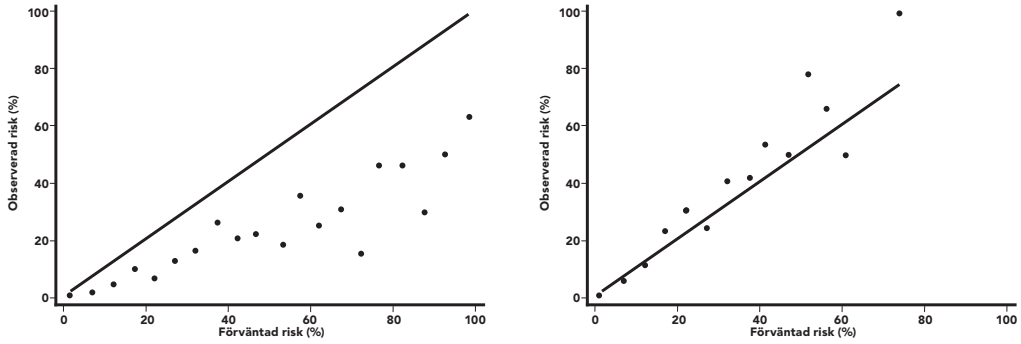
poor initial treatment could incorrectly be attributed to having sicker patients. This aspect and the fact that in the mid 90´s a license fee had to be paid for using the PRISM made it less popular and stimulated other scoring systems to be developed elsewhere.

The Paediatric index of mortality score, PIM

In an attempt to develop a mortality prediction model less sensitive to poor initial patient management a mortality prediction model based on UK and Australian cohort data was developed out of initially eight "explanatory variables" collected at the time of admission. It was named the Paediatric Index of Mortality (PIM). This logistic regression model was based on cohort data from 5,695 PICU patients and was published in 1997.[43] It was further developed into the very popular PIM2[44] published in 2003 based on 20,787 patients from New Zealand, Australia and UK. PIM2 rendered worldwide recognition. The latest version of PIM, the PIM3[45] was published in 2013 and is based on 53,112 PICU patients from 60 ICUs in Ireland, UK, Australia and New Zealand admitted in 2010-2011. In Sweden the PIM3 has been adopted by the Swedish intensive care registry (SIR) since 2016 and many PIM3 calculators can be found online.

PIM3 is calculated as follows:
PIM3 score = (3.8233 × pupillary reaction) + (−0.5378 × elective admission) + (0.9763 × mechanical ventilation) + (0.0671 × [absolute {base excess}]) + (−0.0431 × SBP) + (0.1716 × [SBP2/1,000]) + (0.4214 × [{FiO2 × 100}/PaO2]) − (1.2246 × bypass cardiac procedure) − (0.8762 × non-bypass cardiac procedure) − (1.5164 × noncardiac procedure) + (1.6225 × very high-risk diagnosis) + (1.0725 × high-risk diagnosis) − (2.1766 × low-risk diagnosis) − 1.7928.
Probability of death = exp (PIM3 score)/[1 + exp (PIM3 score)].

Since the standardized mortality ratio* (SMR) has drifted due to medical development and most countries have a SMR below 1, different countries "calibrate" their PIM score so the country PIM scores fit a SMR of 1. In the figuer below from the Swedish intensive care registry you can see PIM2 before (left) and after calibration (right) 2012. The coefficient – 4,8841 (for PIM2) in the end of the calculation, is changed and all the other coefficints multiplied with the same factor. The goal to have a so called Cox´slope 1,00 after calibration.



** Standardized mortality ratio, (SMR) is: observed mortality / expected mortality (calculated from the from the PIM2 score)*

If the same version or "calibration" of the PIM score formula is used, you can compare outcome between countries and PICU wards. One need to keep this in mind when comparing PIM score levels between countries (or wards).

The Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry

During the 80´s and 90´s a structured approach to evaluation of PICU outcome had developed. Parallel to the scoring systems, groups were formed to support intensive care units. One of these groups were The Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry.[46] It was established by the Australian and New Zealand Intensive Care Society (ANZICS) Paediatric Study Group in 1997 with three aims:

- To describe paediatric intensive care practices and outcomes in Australia and New Zealand.
- To provide contributing units with efficacy and efficiency reports that compare performance in their units against national and international standards.
- To facilitate research in paediatric intensive care.

One of the ANZPIC registry utilities is the admission diagnostic codes. This tool is used when reporting admitted patients (in Australia and New Zealand) to the registry but can also be used to stratify cohort data to elucidate reason for PICU admission. In the studies presented in this thesis both cohorts were stratified according to these admission diagnostic codes.

Outcome and centralisation

In the -90s´, the technical development of ventilators and general ICU care had given most AICUs the possibility to not only treat adults but also children in ventilatory distress with ventilators. Now, without the need to make adjustments to the ventilator construction to suit the paediatric patients. The possibility to measure ICU mortality and SMR, since mortality prediction tools were readily available, together with development of patient transport systems, stressed the fact that big differences in outcome between non tertial hospitals and specialized units was no longer acceptable and could be overcome by transfer of patients to specialised units.[47-50]

Both the American College of Critical Care Medicine and the Society of Critical Care Medicine were obligated to endorse the principal of regionalisation of PICU care. Although the UK had been trying to centralise PICU care the situation was still fragmented.

An epic study was published 1997 in the Lancet by Gael Pearson and Frank Shann[51] were ICU mortality rate was compared between The Trent Health Authority, UK, and the state of Victoria, Australia. The regions had comparable populations with slightly over four million inhabitants but in Victoria the PICU care was centralized and in Trent it was scattered.

The study showed, both with PRISM and PIM score, a twofold, 2.07 odds ratio for

death of children in Trent relative to Victoria. In Trent only the PICU at the Birmingham Children's Hospital showed less than expected deaths. The study reverberated through the UK and in Sweden a discussion started on where to treat children in need of intensive care and if to centralize, was there a sufficient number of beds? The stage was set for a Swedish study.

The current ICU situation in Sweden.

During the time of the studies presented in this thesis, there were three specialized paediatric intensive care units, PICUs in Sweden. They were (and still are) located in Stockholm, Lund and Gothenburg. They care for children no younger than 32 gestational weeks and up to 16 years of age (patients with medical conditions can be up to 18 years of age). Today, a fourth PICU recourse is located together with the AICU of Uppsala Akademiska Sjukhus. Adult Intensive care units in Sweden were 78 at the time of the first study but have since then through reorganization become 80. There are specialized ICUs; eight thoracic (THIVA)-, five neuro (NIVA)-, two infections (infektions-IVA)-, two burn (BrIVA)- and one ECMO-ICU. A total of 516 available ICU-beds were reported in 2017 (ref SIR yearly report 2017).[17]

Limitation of medical treatment, LOMT

All patients might not benefit from every possible medical treatment or strategy. A commonly used strategy in Sweden is to adjust the level of treatment according to the clinical and ethical situation. In contrast to adults, a child mostly cannot give voice to their own wishes and decisions, these discussions therefore mostly are performed together with the parents. To reach a decision concerning the best level of care for a specific patient mostly requires a structured discussion among colleagues and parents. Once a decision is formed it will be noted into the patients' medical journal. In Sweden, in contrast to many other countries, it is the doctor treating the patient (in cooperation with other involved specialties) that makes the final decision concerning the level of care. To limit, withdraw or withhold medical treatment comes with different names in different countries and cultures[52] In Sweden, the commonly used term is "limitation of medical treatment", LOMT. To be legally valid, and not lost in staff shift reports, there is a standardized document in the patient journal where responsible clinician concludes the situation of the patient, the decision(s) made, specialists involved in the discussion, time and date. Any possible treatment strategy, modality and level can here be decided upon. Previously, the frequency of LOMT has not been known among children who die the coming years after PICU discharge.

3 AIMS

The overall objective of this thesis was to determine the need for Swedish pediatric intensive care and to deepen field-specific knowledge regarding the children admitted to PICU/ICU care by describing effects on short-term and long-term outcomes.

Specific aims were:

1. To determine the total number of children yearly admitted to ICU care in Sweden.
2. To describe PICU mortality in Sweden.
3. To describe Long term mortality (5-year).
4. To compare Swedish PICU outcome with published data through PIM2.
5. To evaluate factors involved in long-term outcome.
6. To evaluate the need for arterial blood gas in the PIM2 calculation.
7. To determine if limitations of medical treatment (LOMT) limited readmission for children not readmitted to PICU when becoming terminally ill.

4 METHODS

Paper I

Study design

A national, closed cohort was formed of all paediatric patients between six months and 16 years of age admitted either to one of the three PICUs or to an adult ICU in Sweden between March 15, 1998 and March 14, 2001. A second data collection of the same parameters was made from all PICUs including all infants 1 to 6 months of age admitted to a PICU during the same time. For practical reasons data on that age group were not retrieved from the adult ICUs. Data on gender, age, time of admission and discharge, rout of admission was collected.

The main ICD-10 diagnosis stating the reason for index PICU admission was used to assign each patient to one of seven main admission diagnostic groups. These groups were compiled applying the uniform diagnostic coding system used in the Australia and New Zealand Paediatric Intensive Care (ANZPIC) Registry.[46] All patients had one or multiple valid ICD-10 diagnoses registered during their PICU admission.

Diagnostic groups

The diagnostic groups consisted of Injury (Inj), Neurological (Neuro), Postoperative (Post Op), Cardiovascular (CVS), Gastrointestinal/Renal (GI), Respiratory (Resp), and Miscellaneous (Misc). The Misc group included sepsis, post-cardiac arrest, malignancies, endocrine disorders, and allergic reactions in accordance with the recommendations for the ANZPIC registry. Adjustments had to be made for the retrospective nature of the coding; for example, the ANZPIC registry group "Postoperative Cardiovascular" had to be included in the CVS group as it was not possible to differentiate post-operative admissions from other admissions with CVS diagnoses. The diagnoses Postoperative ENT/Thoracic, Postoperative Neuro, and Postoperative Other were all included in one group termed Postoperative (Post Op).

ICU was defined as an ICU with resources to treat patients with intubation and mechanical ventilation for more than 24 h, a definition used previously in ICU epidemiological studies.[53] In this study, exposure was defined as admittance to intensive care and outcome defined as survival up to 5 years post the last registered ICU admission during the study period.

Survival calculation

Vital statistics for each patient (dead or alive up to 5 years after inclusion) were obtained from the File of National Registration 6 months after the study endpoint of 14 March

2006 to allow for the file to be accurately updated. To compare the cohort with the background natural mortality, a comparison of vital data for all children living in Sweden not exposed to ICU care and of the same ages and for the same time period was also made.

Paper II

Study design

A new national, prospective, closed cohort was set up between January 1, 2008 and December 31, 2010. All pediatric patients up to 16 years of age with Swedish 10-digit personal identity numbers admitted to one of the three Swedish PICUs were included in the study. During the study period, specialized PICU care was carried out at three locations in Sweden. These included The University Hospital of Lund, The Queen Silvia Children's Hospital at Sahlgrenska University Hospital of Gothenburg, and the PICU and ECMO Centre's of Astrid Lindgrens Children's Hospital at Karolinska University Hospital in Stockholm.

The first noted admission during the study was defined as the index admission. Survival within the cohort after PICU index admission was checked through the File of National Registration 54 on January 1, 2012, resulting in an assessment after at least one but up to four years post index admission. For each patient, the following data were collected: personal identity number, PICU admission diagnosis (ICD-10), PIM2, and time and source of admission and discharge.

Patient groups

Similar to our first study (Paper I) depending on admission diagnosis, every patient was assigned to one of seven admission diagnostic groups. The diagnostic groups consisted of Injury (Inj), Neurological (Neuro), Postoperative (Post Op), Cardiovascular (CVS), Gastrointestinal/Renal (GI), Respiratory (Resp), and Miscellaneous (Misc).[16.]

Patients were then assigned into two groups depending on the presence of a single admission (SADM) or multiple admissions (MADM) to the PICU. Patients with more than one admission were assigned to early or late readmission groups in conjunction with earlier studies.[55,56] Early readmission was defined as being readmitted within 48 hours of discharge from PICU, while late readmission was defined as being readmitted after 48 hours post PICU discharge.

In accordance with the praxis of European Medicines Agency (EMA) for children,[57] five different age groups were also formed: 0–2 days, 3–28 days, >28 days–2 years, >2–12 years, and >12–16 years. The age-group affiliation for each patient was decided by patient age on index admission.

Complex Chronic Conditions

When finalizing the study, we were made aware of the possible impact of complex chronic conditions (CCC) in the PICU population. We therefore added data regarding the presence of a CCC and CCC subcategories into the dataset. The updated list of complex

chronic conditions version 2 (CCCv2) with 10 subcategories was used. No patient was assigned to the 11th group, "Premature and Neonatal." Complex chronic conditions (CCCs) were initially defined by Feudtner,[58] further explored in the PICU population by Edwards[59] and updated to the CCCv2 by Feudtner.[60] Combining the presence of a CCC with sorting by reason for PICU admission according to the ANZPIC system, allowed us to describe the data related to underlying chronic morbidity and permitted us to indicate which acute event made PICU care necessary.

Data collection and validation

For each patient, the following data were collected: personal identity number, PICU admission diagnosis (ICD-10), PIM2, and time and source of admission and discharge. All admissions were checked for the presence of a CCC and a CCC subcategory. If more than one CCC was present, the first noted was used for CCC subcategory classification. The PIM score was verified through an extensive check of data validity by two experienced pediatric intensivists. All admissions were checked for accuracy regarding the time of admission and discharge. After extensive verification of the admission data, 449 temporary so-called "reserve numbers" could be converted to valid personal identity numbers, and 51 non-Swedish citizens were identified and excluded from the study. The personal identity numbers of the patients in the cohort were sent to the Swedish File of National Registration[54] to obtain survival data. The Swedish File of National Registration keeps a governmental-controlled registry of all Swedish citizens, including date of birth and date of death. PICU mortality risk and standardized mortality risk (SMR) were calculated using the PIM2 (2003) model.[2] The Swedish Intensive Care Registry (SIR)[17] has continuously collected admission data and subsequent PIM scores for all Swedish PICU patients since 2007. Because this process was under implementation during the time of this study, data for our investigation were collected directly from each PICU.

Statistics

The PICU mortality for each diagnostic, age, or admission group was calculated. Mortality outside the PICU was calculated for the SADM and MADM groups respectively. Long-term survival was expressed as Kaplan-Meier (KM) curves for the single or multiple admission groups and, for the four groups, single or multiple admission with or without a CCC present. Censoring was carried out by January 1, 2012 or at the time of death. Differences between curves and the hazard ratio were examined by using both Log-rank (Mantel-Cox) and Gehan- Breslow-Wilcoxon tests. Likewise, differences between KM curves of single or multiple admissions for the diagnostic subgroups were evaluated. Differences were considered statistically significant when $p<0.05$; for multi-group comparison of the curves of SADM and MADM with or without CCC, $p<0.0083$ was considered statistically significant after Bonferroni correction ($K = 6$). Mortality rates (MR) for the different admission diagnostic groups were calculated (total number of deaths during time of follow-up divided by total accumulated person-time during follow-up), expressed

as deaths per year of follow-up time. Patient follow-up time was accumulated from start of index admission to censoring. Mortality rate ratios (MRR) between admission group mortality rates were calculated (MR SADM / MR MADM).

The PICU follow-up data, KM curves, MR, and MRR have been illustrated. Descriptive statistics, curves, and survival calculations were carried out using MS Excel (Microsoft Corporation, Redmond, Washington, USA) and GraphPad prism 5.4 (GraphPad Software Inc. San Diego, USA). Data are given as median values and inter quartile range (IQR).

Paper III

Study design

Due to data formative reasons in this study only a subset of data from the cohort gathered in paper II could be included, namely the data from patients consecutively admitted to the PICU in the Queen Silvia Children's Hospital (DSBUS) from January 1st 2008 to December 31st 2010. The PICU is one of two centers in Sweden for paediatric cardiac surgery and has a case mix with approximately 50% cardiac cases.

As in paper I and II all admissions were classified into seven different diagnostic groups in accordance with the Australian New Zeeland Paediatric Intensive Care, (ANZPIC) registry (4). This time a separate group called non-Respiratory was formed containing all the groups but the Respiratory patients.

The impact of the PaO2/FiO2 ratio on the PIM2 score and its derived probability was estimated in patients with available PaO2 data at admission by comparing the PIM2 score estimated with and without PaO2 data.

The difference in predictability between the non-respiratory and respiratory groups was tested without arterial blood gas data included in the PIM2 calculation.

Standardized mortality ratio (SMR) for the study group and the diagnostic subgroups respiratory and non-respiratory was also explored and presented. The groups with and without arterial blood gas data present were also compared.

Statistics

Tests for correlation between PIM2 scores estimated with and without arterial blood gas data and probability estimated with and without arterial blood gas data were performed by the Spearman rank correlation.

Bias, expressed as percentage mean prediction error (MPE%) and precision, expressed as percentage root mean square prediction error (RMSE%), were calculated as outlined by Sheiner and Beal.[61] The Mann-Whitney U-test was used to analyse differences between two unrelated observations.

The variance ratio test was used for the comparison of the variability of data in two populations, for example in the non-respiratory and respiratory groups. Classified data from two independent populations were compared by the Fischer exact test.

Standardised mortality ratio (SMR) and its 95% confidence intervals were calculated as given by Liddell (62). Data are presented as median values and inter quartile range (IQR) unless otherwise stated.Statistics were evaluated by MS Excel (Microsoft Corporation, Redmond, Washington USA) and Graph Pad Instat 3.10 (Graph Pad Software inc. San Diego, USA). All reported p-values were from two-sided tests and considered statistically significant if $p < 0.05$.

Paper IV

From the cohort formed and studied in paper-II a sub-analysis was made in the 268 children that died in the years after PICU discharge. For these children medical records were checked for presence of LOMT decisions and statements regarding yes or no to PICU readmission. The children were grouped according to place of death; after being readmitted to a PICU (PICU group), or in Hospital (Hospital group) or at home (Home group). In the PICU group presence of any sort of LOMT in the records was noted as presence of a LOMT. For the Hospital and Home groups LOMT was noted if containing no readmission to PICU. Gender, age, survival time, admission diagnostic group and presence of a chronic complex condition (CCC)[21, 22] were identified.

Ethical considerations

The Central Ethical Review Board at the Karolinska Institute approved this nationwide study after consulting with the regional boards at Gothenburg and Lund [Dnr 02-483] (Paper I). For the second cohort, (paper II-IV) extended ethical approvals were sought and subsequently granted [Dnr 2007/1073-32, Dnr 2008/39-32, KI-Dnr 2009/1295-32. KI Dnr 2016 /2274-32].

5 RESULTS

Paper I

ICU admission, demographics and LOS

Of the eligible ICUs, 70 (86%) participated. A total of 8063 admissions were recorded for the 3-year period by 6661 individual patients *(Table 1)*.

Number of admissions, demographics.

	Number of admissions	Number of patients*	Age median (years)	LOS median (days)	LOS >3 days	ICU mortality	5-year mortality
All admissions	8063	6661	6.1	1	1038 (13%)	140 (2.1%)	366 (5.6%)
PICU ($n=3$)	3561	2755	2.1	1	661 (19%)	69 (2.5%)	201 (7.3%)
PICU age 1–6 months	926	650	0.2	2	268 (29%)	20 (3.1%)	61 (9.4%)
PICU age 6 months–16 years	2635	2105	4.8	1	393 (15%)	49 (2.3%)	140 (6.6%)
Adult ICU ($n=52$)	4502	3906	9.5	1	377 (8%)	71 (1.9%)	165 (4.3%)
University ICU ($n=10$)	1675	1390	8.5	1	240 (14%)	43 (3.1%)	107 (7.7%)
General ICU ($n=42$)	2827	2516	9.9	1	137 (5%)	28 (1.2%)	58 (2.4%)

LOS and mortality for different groups.
*In mortality and LOS calculations, 87 patients (in a general ICU) are excluded as they lack dates for ICU admission.
LOS, length-of-stay; ICU, intensive care unit; PICU, paediatric intensive care unit.

Table 1 Demographic data

Of these, 650 were infants between 1 and 6 months of age, with 926 admissions to PICU. The estimated loss of data were approximately 400 admissions (see 'Methods'). Eight hundred seventy-two patients (13%) had two or more admissions during the period. Of the multiple admissions, 213 were re-admissions to the same ICU within 2 days and 165 were transfers between ICUs in different hospitals. Sixty-five of the inter-hospital transfers were from an adult ICU to a PICU. The rate of re-admission within 2 days was 2.7%, 3.5% in PICU and 2.0% in adult ICU. The median LOS was 1 day, both for PICUs and adult ICUs *(Table 1)*. Of all PICU admissions, 46% had a LOS of more than 1 day and

FIgure 1A AICU

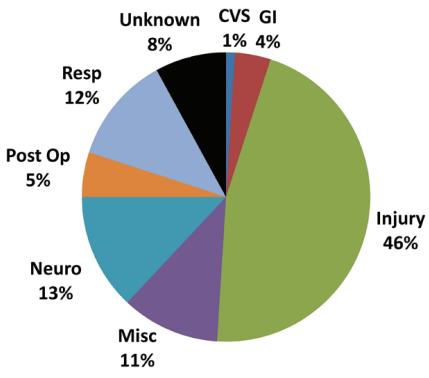


Figure 1B PICU

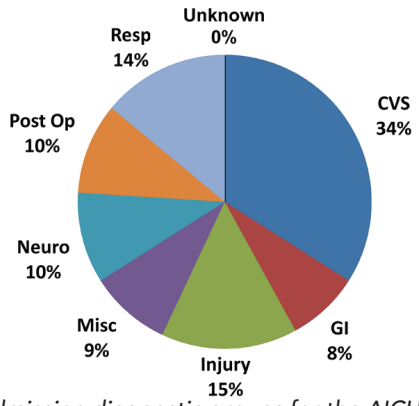


Figure 1A and 1B demonstrating % of different admission diagnostic groups for the AICU and PICU groups.

19% 43 days. The corresponding number for adult ICUs was roughly half, 23% and 8%, respectively. The median age was 6.1 years for all admissions. In PICU, the median age was 2.1 years for all patients and 4.8 if only patients older than 6 months were included; the corresponding age for adult ICU was 9.5 years. Of all the patients admitted to PICU, 46% were females and 54% were males. In adult ICUs, 44% were females and 56% were males. The difference in diagnostic panorama Is presented in *figure 1A and B*.

A clear difference could be seen in diagnostic panorama with the adult ICU having Injury and PICU having cardiovascular as the dominating admission diagnosis. All patients were followed-up for up to 5 years. A total of 366 patients had died, resulting in a 5-year mortality of 5.6%. The mortality during the last registered ICU admission was 2.1% (Table 1). Among these, we found 4.2% mortality (6/142) for re-admission and 4.4% mortality (6/135) after transfer to the last registered admission. The all over mortality for the cohort in the fifth year after admission was still 0.28%, compared with the expected yearly mortality of 0.013% in a non-ICU-exposed comparable cohort of children. For the different diagnostic groups, the 5-year mortality and the immediate ICU mortality (in parenthesis) were Injury 2.2% (1.0%), Miscellaneous 15.8% (6.0%), Respiratory 9.4% (2.4%), Neurological 8.3% (2.9%), CVS 6.5% (2.1%) and GI 5.6% (2.4%). For the post-operative patients, as a group, the 5-year mortality was 4.1% and the ICU mortality was 0.2%. The youngest patients had the highest mortality. For infants 0-6 months old the mortality was 9.4% (3.1%); in the age range of 6 months–1 year the mortality was 7.7% (3.6%), compared with 5.1% (2.0%) for the other age groups together. The overall 5-year mortality in PICU was 7.3%, and the corresponding number for the adult ICU was 4.3%.

Paper II

Patient demographics

During the inclusion period of 36 months, 5,019 admissions were made by 3,688 individuals with complete personal identity numbers. A majority of the patients, 79% (n=2,909) had only one PICU admission, SADM, while 21% (n=779) of the patients had two or more admissions, MADM. This yielding a total of 2,110 (42% of total admissions). The median length of stay (LOS) was 1.3 days (IQR 0.8–3.7 days), and 28.1% of all admissions had a LOS of more than three days. Not surprisingly more admissions were made by males (56.8%) than females (43.2 %), and the same proportions of males (56.9%) and females (43.1 %) were seen among individuals admitted. There was a 5.3% loss to follow up since 196 admitted Swedish children had incomplete personal identity numbers or reserve numbers and could not be identified in the Swedish File of National Registration.

Admission diagnostic and age groups

The overall distribution of diagnostic groups at admission was CVS 39%, Resp 20%, Misc 14%, GI 10%, Neuro 10%, Inj 5%, and Post Op 2%. Groups Inj and Post Op combined included only 279 admissions.

The median age among patients was 8.7 months. There were 304 admissions (n=288)

of patients between 0 and 2 days of age, 754 admissions (n=805) from over 2 days up to 2 months of age and 2208 admissions (n=1195) from over 2 months up to 2 years of age. There were only 400 admissions (n=332) over 12 years of age. Age groups, LOS, and PICU mortality are presented in *Table 8*.

PICU mortality, SADM, MADM, and CCC survival

The PICU mortality for the cohort was 2.8 % (140 deaths in 5,019 admissions). In the diagnostic groups, the PICU mortality was as follows: Misc 8.9%, Neuro 4.5%, Resp 3.2%, GI 2.7%, CVS 2.1%, Inj 1.8%, and Post Op 0.0%. The group of SADM patients (n=2,909) had a PICU mortality of 3.0% (n=88), while the group with multiple admissions (n=779) had a mortality of 6.7% (n=52) on subsequent admissions. A significant difference was also seen in survival over time between single and multiple admissions groups, *Fig 2*.

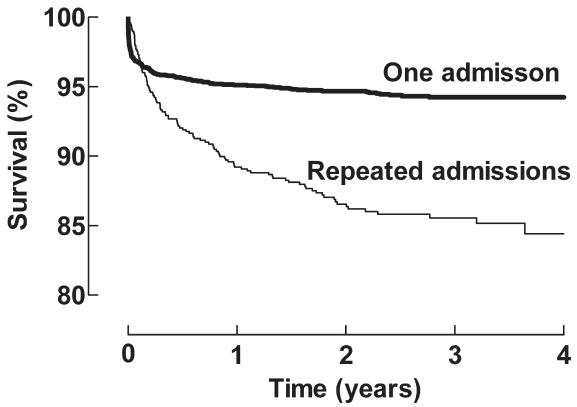


Fig 2. Cumulative survival for the single and multiple admission groups.
Statistically significant differences between curves are as follows: Hazard Ratio 3.28; 95% CI 2.43–4.44, Log-rank (Mantel-Cox) or Gehan-Breslow-Wilcoxon Test, both p<0.0001.

A CCC was present in 46.8% (1,728 of 3,688) of the patients. In the group of MADM patients with CCC, 16.2% (82 of 507) of the patients died, which represented 75.2% (n=90) of all the deaths in the MADM group. In the group of SADM with a CCC, 7.5% (92 of 1,221) of the patients died, which represented 57.5% (n=160) of all deaths in the SADM group. The cumulative survival for SADM and MADM patient groups with or without a CCC is presented in *Fig 3*; p-values are provided in *Table 2*.

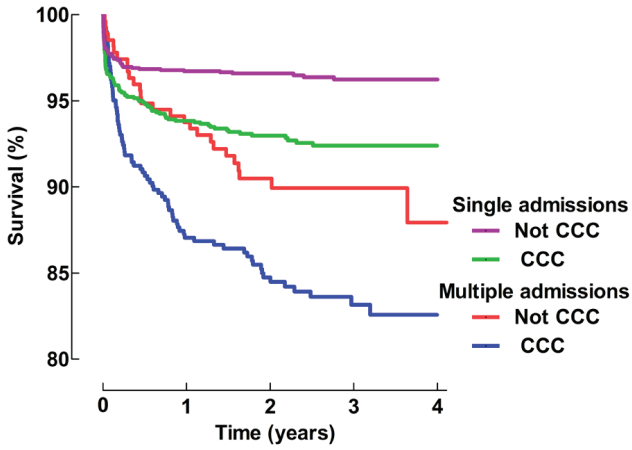


Fig 3. K-M curves for patients with single admissions (SADM) and multiple admissions (MADM) with or without a complex chronic condition (CCC).

Subgroup		*Subgroup*	*p-values (Log-rank (Mantel-Cox) Test)*	*p-values (Gehan-Breslow-Wicoxon Test)*
MADM + CCC	vs	MADM Not CCC	0.0208	0.0166
MADM + CCC	vs	SADM + CCC	<0.0001	<0.0001
MADM + CCC	vs	SADM Not CCC	<0.0001	<0.0001
MADM Not CCC	vs	SADM + CCC	0.1674	0.2982
MADM Not CCC	vs	SADM Not CCC	<0.0001	<0.0001
SADM + CCC	vs	SADM Not CCC	<0.0001	<0.0001

Values of p<0.0083 were considered statistically significant after Bonferroni correction (K=6).

Table 2. p-values for comparison between patients with single (SADM) or multiple (MADM) admissions with or without a complex chronic condition (CCC).

SADM, MADM and MR for admission diagnostic groups

The impact of SADM and MADM was explored in detail for the diagnostic groups. The results are presented in *4a and 4b*.

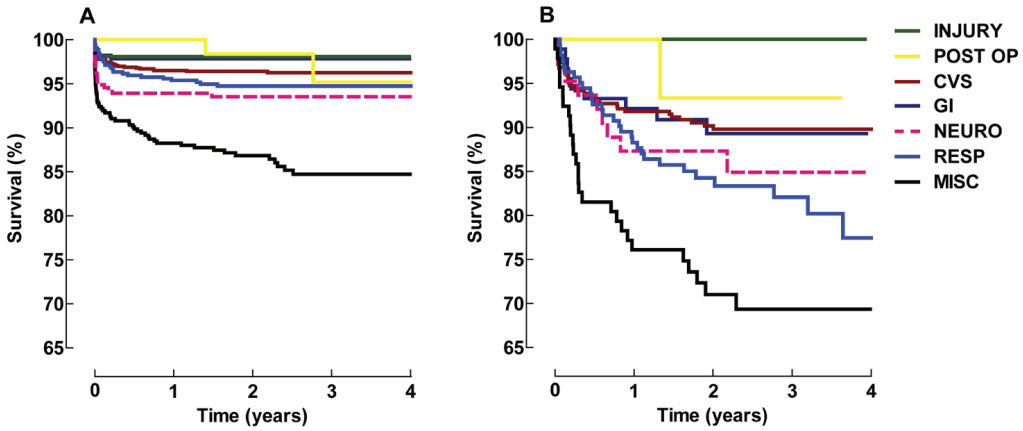


Fig 3. Kaplan-Meier plots showing diagnostic group survival on single admission (a) and multiple admissions (b). There was a difference (p<0.001) between single and multiple admissions in all of the diagnostic groups except Inj and Post Op. Neuro displayed a p=0.04. All p-values are presented in Table 9.

PICU mortality, mortality rate, and mortality rate ratio

Total patient follow-up time during the study was 8,688 patient years, accumulated from the start of each index admission. Median follow-up time was 2.6 years (IQR 1.65–3.25) for patients with single admissions and 2.5 years (IQR 1.6–3.3) for patients with multiple admissions. The total mortality in the cohort during the time of the study was 268 individuals and corresponded to a MR of 0.023 in the single admission group and 0.062 in the multiple admissions group giving an MRR value of 2.69. MR and MRR for all diagnostic groups presented in *Table 3*.

Single admission

ANZPIC

Diagnostic group	All groups	CVS	GI	Injury	Neuro	Post op	Resp	Misc
Numbers of patients	2,909	1,087	279	209	312	70	518	434
PICU mortality n (%)	88 (3.0)	22 (2.0)	5 (1.8)	4 (1.9)	13 (4.2)	0 (0.0)	11 (2.1)	33 (7.6)
Mortality rate								
Deaths/person years	0.023	0.015	0.009	0.008	0.027	0.011	0.021	0.066

Multiple admission

ANZPIC

Diagnostic group	All groups	CVS	GI	Injury	Neuro	Post op	Resp	Misc
Numbers of patients	779	342	89	15	63	15	163	92
PICU mortality n (%)	52 (6.7)	19 (5.6)	5 (5.6)	0 (0.0)	3 (4.8)	0 (0.0)	11 (6.7)	11 (12)
Mortality rate								
Deaths/person years	0.062	0.039	0.042	0.000	0.191	0.029	0.107	0.141
Mortality Rate Ratio	2.69	2.59	4.78	0.00	7.07	2.50	5.07	2.16

n=number of patients in group, MR=mortality rate (total number of deaths during time of follow-up, divided by total accumulated person-time during follow-up), expressed as deaths per person-years of follow-up time. MRR=mortality rate ratio (MR SADM / MR MADM).

Table 3. PICU mortality and mortality rate (MR) with mortality rate ratio (MRR) for single (SADM) and multiple (MADM) admissions groups, depending on admission diagnostic group.

SADM and MADM with and without CCC in subcategories

To conduct a more in-depth analysis of subgroups, the mortality in the different diagnostic subgroups with and without CCC is presented in *Tables 4 and 5* below.

	Patients with Multiple Admissions		***Patients with a Single Admission***	
	All	Deceased	All	Deceased
Numbers of patients	272	27 (9.9%)	1,688	68 (4.0%)
Median age years (mean)*	0.5 (3.0)	0.4 (3.4)	0.4 (3.2)	1.3 (4.5)
Male sex (% of total)	172 (63%)	19 (11%)	1,156 (57.9%)	40 (3.6%)
ANZPIC diagnostic groups				
Cardiovascular	41	4 (9.7%)	319	12 (3.7%)
Respiratory	93	11 (11.8%)	412	15 (3.6%)
Miscellaneous	35	4 (11.4)	207	19 (9.2%)
Neurological	36	3 (8.3%)	252	11(4.3%)
Gastrointestinal/Renal	43	5 (11.6%)	226	5 (2.2%)
Postoperative	10	0	67	2 (3.0%)
Injury	14	0	205	4 (1.9%)

** Both median and mean age are presented to illustrate skewed distribution.*

Table 4. MADM and SADM patients without CCC and deaths in admission diagnostic groups.

	Patients with Multiple Admissions and a Complex Chronic Condition		Patients with a Single Admission and a Complex Chronic Condition	
	All	Deceased	All	Deceased
Number of patients	507	82 (16.2%)	1221	92 (7.5%)
Age years, median (mean)*	0.1 (1.6)	0.3 (2.4)	1.0 (3.5)	0.7 (3.3)
Male sex (% of total)	276 (54.4%)	40 (14.5%)	675 (55.3%)	53 (7.8%)
ANZPIC diagnostic groups				
Cardiovascular	302	30 (9.9%)	768	28 (3.6%)
Respiratory	69	18 (26.0%)	106	12 (11.3%)
Miscellaneous	56	23 (41.0%)	227	42 (18.5%)
Neurological	27	7 (25.9%)	60	9 (15.0%)
Gastrointestinal	47	4 (8.5%)	53	1 (1.9%)
Postoperative	5	1 (20%)	3	0
Injury	1	0	4	0
Complex Chronic Conditions				
Subcategories	507	82 (16.2%)	1,221	92 (7.5%)
Age years, median (mean)*	0.1 (1.6)	0.3 (2.4)	1.0 (3.5)	0.7 (3.3)
Male sex	276 (54.4%)	40 (14.5%)	675 (5.5%)	53 (7.8%)
Cardiovascular	308	35 (11.4%)	761	29 (3.8%)
Respiratory	21	2 (9.5%)	47	4 (8.5%)
Neuromuscular	34	9 (26.4%)	82	12 (14.6%)
Congenital/genetic	44	6 (13.6%)	84	6 (7.1%)
Oncologic	40	19 (47.5%)	106	29 (25.5%)
Metabolic/endocrine	14	6 (42.8%)	88	8 (9.0%)
Renal	8	2 (25%)	12	1 (8.3%)
Gastrointestinal	24	1 (4.2%)	35	2 (5.7%)
Hematologic/immunologic	5	2 (40%)	3	1 (33.3%)
Miscellaneous**	0	0	3	0

** Both median and mean age are presented to illustrate skewed distribution.*
*** Miscellaneous includes rheumatologic, orthopedic, and psychiatric conditions.*

Table 5. MADM and SADM patients with CCC and deaths in ANZPIC admission diagnostic groups and CCC subcategories.

Readmission characteristics

Among all admissions, there were 1,331 (26.5%) readmissions, of which 327 (24.6%) were readmissions within 48 hours from the previous discharge. The median time to readmission in this group was 22 hours (IQR: 8–28 hours), of which 1,004 (75.4%) readmissions occurred more than 48 hours after previous discharge with a median time of 48 days (IQR: 11–160 days). The rate of readmission, counting only early readmissions, was 6.5%. PICU readmission mortality was 6.4% (in 21 out of 327 readmissions) in this group and 3.2% (in 31 of 1,004 readmissions) in the late readmission group. The median age was 3.4 months (IQR: 0.5–20 months) in the early group and 8.5 months (IQR: 3.5–28 months) in the late group. In Swedish PICU facilities, (re)admissions are not classified as scheduled or unscheduled. Deaths among MADM patients—according to diagnostic group, early or late readmissions, PICU status, or final PICU stay—are presented in *Table 10,* page 32.

Impact of having an increasing number of PICU admissions

When MADM patients were analyzed regarding number of PICU admissions, they demonstrated between two and 14 admissions during the time of study. The majority of patients had two (64.3%) or three (20.5%) admissions. Only nine children in total had more than eight admissions. Details regarding presence of a CCC and mortality in the patients (depending on the number of admissions) are presented in *Tables 6 and 7* below.

Number of admissions	**2**	**3**	**4**	**5**	**6**	**7**
Individuals n (%)*	501 (64.3)	160 (20.5)	55 (7.0)	32 (4.1)	9 (1.2)	7 (0.9)
Complex Chronic Condition n (%)	306 (61)	105 (65.6)	36 (65.5)	20 (62.5)	7 (77.8)	3 (42.9)
Deaths n (%)	61 (12.2)	20 (12.5)	10 (18.2)	9 (45)	2 (22.2)	2 (28.6)
Deaths with Complex Chronic Condition n (%)	41 (67.2)	15 (75)	6 (60)	5 (55.6)	1 (50)	0

Table 6. Number of admissions among the MADM patients and presence of CCC and death during the study. 2-7 admissions.

Number of admissions	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Individuals n (%)*	6 (0.8)	3 (0.4)	2 (0.3)	1 (0.13)	1 (0.13)	1 (0.13)	1 (0.13)
Complex Chronic Condition n (%)	5 (83.3)	2 (66.7)	2 (100)	1 (100)	1 (100)	1 (100)	1 (100)
Deaths n (%)	2 (33.3)	1 (50)	0	1 (100)	1 (100)	0	1 (100)
Deaths with Complex Chronic Condition n (%)	1 (50)	0	0	1 (100)	1 (100)	0	1 (100)

*n=number of individual patients, * (%) of 779 MADM individuals.*

Table 7. Number of admissions among the MADM patients and presence of CCC and death during the study. 8-14 admissions.

Transfer to PICU from other ICUs and units

In total, 278 admissions to a PICU were documented as originating from an Adult Intensive Care Unit (AICU) in another Swedish hospital, and 655 admissions occurred from another hospital. In the latter case, it was unclear if these transfers were a referral from an ICU, emergency room, or elsewhere.

Age	0-16y	0-2d	>2-28d	>28d-24m	>2-12y	>12-16y
median age	0.7y (260d)	(0.9d)	9.6d	0.5y (168d)	5y	14.2y
All admissions (n=)	5019	304	754	2208	1353	400
Male/Female	56.8% / 43.2%					
PICU mortality	141 / 5,019 (2.8%)	9 (2.9%)	20/754 (2.5%)	67/2,208 (3.0%)	31/1,353 (2.3%)	14 /400 (3.5%)
LOS PICU median (days)	1.3d	3.3d	2.8d	1.55d	0.95d	0.92d
LOS PICU >3d days (%)	1412 (28.1%)	159 (52.1%)	340 (45.1%)	614 (28.0%)	232 (17.1%)	66 (16.5%)

Table 8 Age groups, LOS, and PICU mortality

Admssion diagnositc group	Survival (%) SADM	No of deaths SADM	Survival (%) MADM	No of deaths MADM	p-value
Inj	98.1	0	100.0	4	0.6183
GI	97.8	9	89.7	6	0.0009
Post op	96.7	1	93.3	2	0.4181
CVS	96.4	31	90.7	40	>0.0001
Resp	94.9	27	81.1	26	>0.0001
Neuro	93.6	9	85.7	20	0.0437
Misc	86.1	26	71.0	59	0.0007

Table 9 table 2 P values for differences between groups presented in Fig 3

Diagnostic group	CVS	Misc	Resp	Neuro	GI	Inj	Post Op
Readmission status (n=)							
Early (<48h), dead in PICU	8	5	4	3	1	0	0
Late (>48h), dead in PICU	11	9	7	0	4	0	0
Dead after PICU discharge	15	14	17	6	4	0	1

Table 10 Deaths among MADM patients — according to diagnostic group, early or late readmissions, PICU status, or final PICU stay

Paper III

We identified 1,793 consecutive admissions (1,255 patients) between newborn infants and 16 years of age. Of the 1,793 admissions, 990 had recorded information of PaO2 and FiO2. These 990 admissions formed the study group.

The ratio females/males were 441/549 and 360/443 in the two groups with and without arterial blood gas data, respectively, p=0.9239.

Patients with PaO2 data available at admission were younger, 0.71 years (0.15 to 3.85 years) and 1.51 years (0.27 to 6.48) for patients with and without PaO2 data, respectively, p<0.0001. The age difference between admission diagnostic groups was only statistically significant for the gastrointestinal group. The age distribution is presented in *Table 11*.

	Age (years)				
	Admissions with		Admissions without		
	PaO2	Number	PaO2	Number	p-value
CVS	0.538 (0.078 to 3.232)	579	0.511 (0.055 to 3.464)	313	0.9337
GI	0.421 (0.062 to 2.546)	101	2.025 (0.269 to 8.562)	92	0.0011
Injur	6.717 (3.154 to 15.35)	20	9.715 (3.324 to 14.06)	38	0.6646
Misc	1.684 (0.485 to 10.71)	116	3.147 (0.739 to 9.744)	129	0.561
Neuro	2.672 (0.974 to 7.11)	32	2.688 (0.988 to 8.476)	79	0.9507
Post Op	10.01 (0.072 to 13.34)	5	9.781 (5.031 to 12.81)	5	1.00000
Resp	0.7143 (0.214 to 4.418)	137	1.335 (0.262 to 4.839)	147	0.1326
All Admissions	0.7078 (0.149 to 3.853)	990	1.511 (0.273 to 6.485)	803	<0.0001

Table 11 Age distribution

The numbers of admissions for the different diagnostic groups with and without PaO2 values available on admission are presented in *Table 12*.

Diagnoses	with PaO2 (n=990)	without PaO2 (n=803)
CVS	579	313
GI	101	92
Injury	20	38
Misc	116	129
Neuro	32	79
Post Op	5	5
Resp	137	147

Table 12. The total number of admissions divided into diagnostic groups and admissions with and without PaO2 present at admission

The influence of arterial blood gas data on the estimation of the PIM2 score and probability are presented in *Figure 5A and 5B*, respectively.

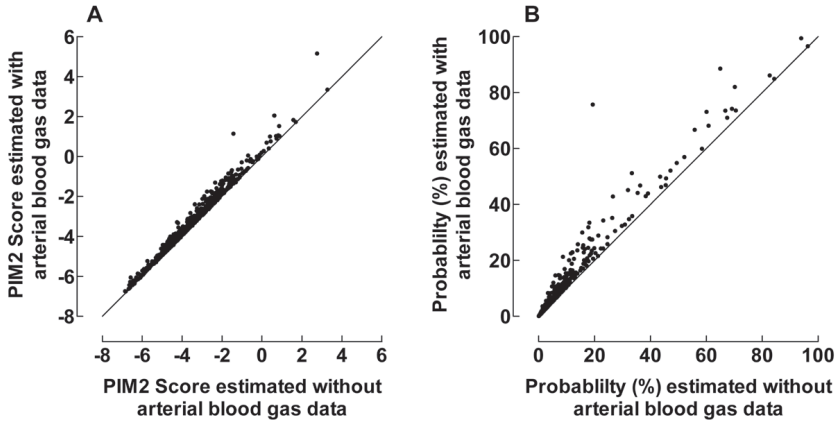


Figure 5A and 5B. Correlation between PIM2 scores and probability estimated with and without arterial blood gas data. Figure 5A shows the influence of arterial blood gas data on the estimation of the PIM2 score. Percentage mean prediction error: –6.148%, percentage root mean square prediction error: 0.266%, Spearman rank correlation coefficient: 0.994.
Figure 5B shows the influence of arterial blood gas data on the estimation of probability. Percentage mean prediction error: 19.499%, percentage root mean square prediction error: 3.055%, Spearman rank correlation coefficient: 0.994.

PIM2 score estimated with and without arterial blood gas data, as well as probability estimated with and without arterial blood gas data, were closely correlated (rs= 0.994 and 0.994, respectively), with a percentage mean prediction error (MPE; bias) of –6.148% and 19.499%, respectively and a percentage root mean square prediction error (RMSE; precision) of 0.266% and 3.055%, respectively.

The influence of excluding arterial blood gas data for estimation of probability is illustrated for the non-respiratory and respiratory groups by plotting the probability, estimated from PIM2 omitting arterial blood gas data, versus PIM2 score estimated with arterial blood gas data, *Figure 6A and 6B*, respectively.

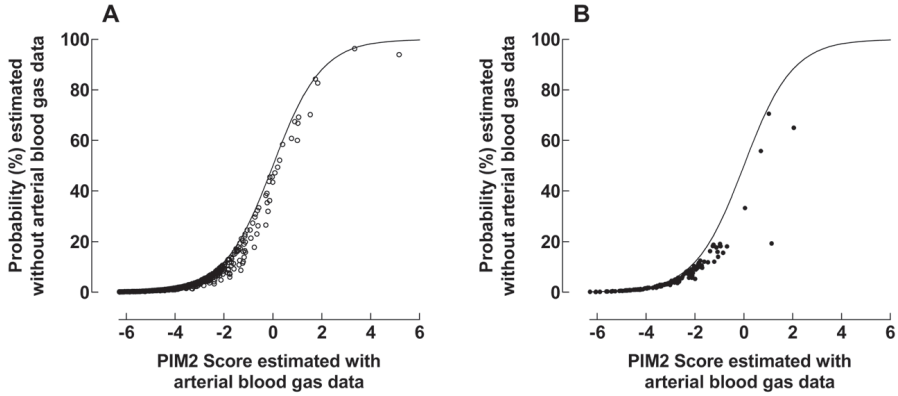


Figure 6A and 6B. Probability, estimated from PIM2 omitting arterial blood gas data, versus PIM2 score estimated with arterial blood gas data.
Figure 6A shows data from patients in the non-respiratory group and Figure 6B shows data from the respiratory group(s). Solid lines show probability predicted for the PIM2 score with arterial blood gas data included.

In the non-respiratory group, we found a close agreement between predicted and true probability despite the fact that arterial blood gas data was omitted. For the respiratory group, important deviations of the predicted probability from the true probability occurred for PIM2 score exceeding –2.20 (probability > 10.0%).

The difference in probability estimated from PIM2 scores with and without arterial blood gas data were larger in the respiratory group as compared to the non-respiratory group ($p<0.0001$). In patients with probability >10%, estimated without arterial blood gas data, the differences in probability with and without arterial blood gas data were 3.161 (1.477 - 6.459) units in the non-respiratory group and 4.397 (2.802 - 9.251) in the respiratory group, respectively. The variability in the respiratory group was significantly larger ($p<0.0001$).

The SMR was slightly but not significantly overestimated by not including arterial blood gas data in the calculation of the PIM2 score, SMR for the two groups was 0.740 (0.515-1.029) and 0.968 (0.591-1.495), respectively, *Table 13.*

	Admissions with PaO2/FiO2 ratio (Study Group)			**Admissions without PaO2/FiO2 ratio**
	All	Resp	Non-Resp	
	N=990	N=137	N=853	n=803
PIM2 estimated with PaO2/FiO2 ratio				
Number of death	35	7	28	
SMR				
(95%CI)	0.606 (0.422 to 0.843)	0.554 (0.222 to 1.142)	0.621 (0.413 to 0.897)	
PIM2 estimated without PaO2/FiO2 ratio				
Number of death	35	7	28	20
SMR	0.740	0.770	0.733	0.968
(95%CI)	(0.515 to 1.029)	(0.308 to 1.586)	(0.487 to 1.059)	(0.591 to 1.495)
p-value	0.4122	0.5099	0.5377	0.3073 (versus All without PaO2/FiO2 ratio)

Table 13. Arterial blood gas data included respectively not included in the estimation of the PIM2 score and subsequent SMR.
PIM2=paediatric index of mortality2, SMR= standardised mortality ratio, FiO2=fractional inspired oxygen, PaO2=arterial oxygen tension, Resp=respiratory, Non-Resp=non-respiratory

To examine the selection bias if the PaO2/FiO2 ratio was required for risk stratification, we examined all 1,793 admissions, stratified by omitting the PaO2/FiO2 ratio from the PIM2 equation and its calculated probability. Patients with the PaO2/FiO2 ratio available had a statistically significantly higher probability than patients without the PaO2/FiO2 ratio available at admission, 1.388 % (0.8361 - 4.049) and 0.7509% (0.4064-2.179), respectively, $p<0.0001$. Data are presented in *Table 14.*

	Probability (%)				
	Admissions	Number	Admissions	Number	p-value
CVS	1.173	579	0.569	313	<0.0001
	(0.824 to 2.401)		(0.406 to 2.149)		
GI	1.317	101	0.598	92	<0.0001
	(0.717 to 2.596)		(0.271 to 1.364)		
Injur	4.240	20	0.829	38	0.0033
	(0.821 to 8.883)		(0.751 to 1.21)		
Misc	1.973	116	0.751	129	<0.0001
	(0.722 to 7.203)		(0.271 to 2.795)		
Neuro	4.030	32	1.022	79	<0.0001
	(1.400 to 8.157)		(0.751 to 2.795)		
Post Op	1.570	5	2.234	5	0.83400
	(1.081 to 2.991)		(1.16 to 10.04)		
Resp	3.312	137	0.751	147	<0.0001
	(1.054 to 8.444)		(0.4064 to 2.795)		
All Admissions	1.386	990	0.751	803	<0.0001
	(0.836 to 4.049)		(0.406 to 2.179)		

Table 14. Probability (%) was calculated from PIM2 estimated without PaO2 in both groups. SMR for the two groups was 0.740 (0.515-1.029) and 0.968 (0.591-1.495), respectively, Table 13.

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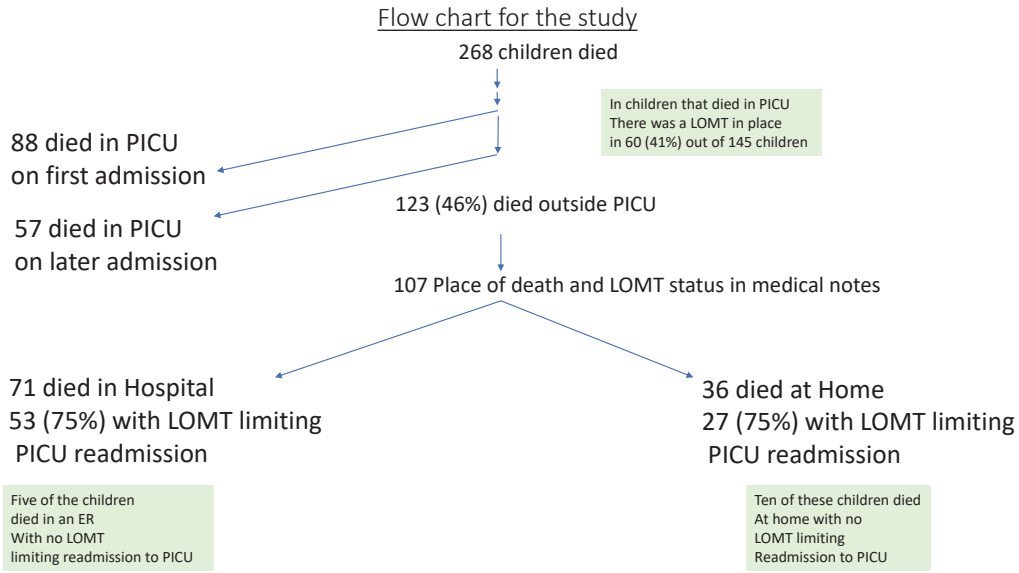

Demographic data for the three groups presented in *table 15* below.

Table 15

Deseaced	PICU	Hosp	Home
n=	145	71	36
cvs	43	21	6
GI	10	2	2
Misc	43	24	16
Neuro	17	7	3
Resp	27	15	9
post op other	1	2	0
Inj	4	0	0
LOS	7.7	8.1	2.8
Admissions	1.8	2.1	1.9
Age years	2.9	3.7	4.3
Male sex (%)	76 (52)	43 (61)	27 (75)

Demographic data, number of children in the three groups, deceased in; PICU, Hospital or at Home. CVS=Cardiovascular, GI=Gastrointestinal/Renal, Neuro=Neurological, Post Op= Postoperative, Resp= Respiratory, Inj= Injury and Misc= Miscellaneous. LOS= length of stay at first PICU admission, Age years= age at first PICU admission, Admissions=average number of admissions for the group during the time of the study.

Survival

A significant difference in survival was seen between the three groups. Presented below as Kaplan- Meier curves in *fig. 7* and significant p-values in *table 16*.

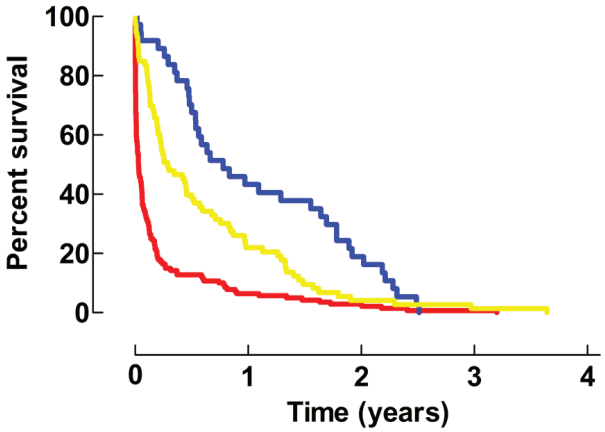

Figure 7
Survival for the three groups over the time of the study. Place of death; red line PICU, yellow line in hospital, blue line at home.

Comparison of Survival Curves	
Log-rank (Mantel-Cox) Test	
Chi square	55,1
df	2
P value	< 0.0001
P value summary	***
Are the survival curves sig different?	Yes
Logrank test for trend	
Chi square	31,59
df	1
P value	< 0.0001
P value summary	***
Sig. trend?	Yes

Table 16
Significant difference between survival curves.

Limitation Of Medical Treatment, LOMT and CCC.

There was a difference in numbers of LOMT limiting PICU readmission and presence of a complex chronic condition (CCC) in the groups. Presented in *fig 8* below.

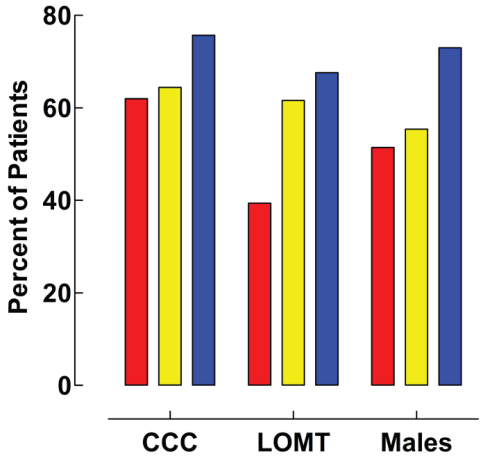

Fig 8.
Presence of CCC and LOMT in the three groups respectively. Place of death; red colour PICU, yellow colour in hospital, blue colour at home.

Admission diagnostic panorama

There was no significant difference in PICU admission diagnostic panorama with regard to place of death. Although there was a trend through the three groups where the children belonging to the CVS and Neuro were most present in the PICU with decreased numbers at home, while the groups Misc and Resp showed the reversed pattern of increased numbers at home. Presented in *fig 9* below.

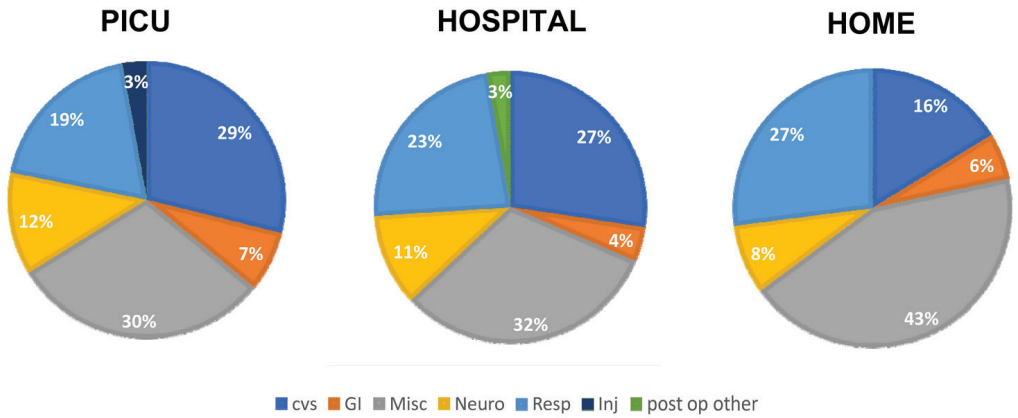

Fig 9. Admission diagnostic groups for the three locations of death, in PICU, in hospital or at home.

Home group, no LOMT, characteristics

Of the children who died at home 9 had no LOMT recorded limiting readmission to PICU. Their mean age was 1.8 years, 5 (50%) had a CCC, 8 (80%) were males, admission diagnostic groups were; Resp 4, Misc 3, CVS 3.

Recorded causes of death were; sepsis 1, H1N1 infection 1, Sudden Infant death 1, cardiac abnormalities 3; (Transposition of the great arteries TGA 1, ventricular septal defect VSD 1, Vitium Organis Cordis VOC unspecified 1), Bacterial pneumonia 1, RS infection 1, viral pneumonia 1, cerebral malformation 1.

Another 5 children in the Hospital group died in an emergency room without any LOMT record limiting PICU readmission. 3 were males, CCC 4, CVS 3, Resp 2, recorded reasons for death; left ventricular hypoplasia 1, pulmonary atresia 1, Vitium organis cordis, VOC unspecified 1, cerebral malformation and acute airway infection 1, respiratory insufficiency 1.

Lost to follow up

In the 17 children that were lost to follow up no clear place of death (n=10) and/or clear LOMT status confirming 'yes' or 'no' to PICU care (n=7) could be identified since records could not be accessed mainly due to technical reasons. There was a CCC present in 13 (76%) of the children and 10 (59%) were males. The disposition of admission diagnostic groups; Misc 5, Resp 5, CVS 4, Neuro 2 and G-I 1. Mean age was 2.3 years, which is slightly younger, and length of stay 9 days which is slightly longer than for the three groups PICU/Hospital/Home.

6 DISCUSSION

At the outset of these studies, the need for ICU care for children in Sweden was not known and neither were prognostic factors for long-term outcomes after PICU discharge or the degree of LOMT at the end of life for the years after PICU care. In order to answer these questions, we had to create two nationwide cohorts and orchestrate a national co-operation. We also asked ourselves if the most painful part of PIM2 -the arterial blood gas sampling could be limited without loss of accuracy.

In Study I,[16] we reported over 8,000 admissions made by over 6,600 children to AICUs (56%) and PICUs (44%) in Sweden. Noted, that children from 0-1months of age in PICUs and that children from 0-6 months in AICUs were not included in the cohort. Children treated in AICUs had very short LOS and most commonly (43%) had the admission diagnosis of "injury", largely due to concussion and alcohol intoxication. An admission diagnosis of post-operative and trauma had excellent long-term outcomes and miscellaneous had the poorest.

Today data from Study I can be compared with Study II and with updated admission data from the Swedish ICU-registry database as accessed online.[17] Data for all children admitted to intensive care from 2015 to 2017 demonstrate 10,893 admissions, where 5,125 (53%) were to a PICU. PIM2 score was not recorded in the first cohort, but PICU and AICU mortality was low (2.5% and 1.9% respectively). PICU mortality reported in Study II was similar at 2.8%. These data seem to correspond with current outcome data from PICU and AICU at 3.0% and 1.5% respectively.[17]

In Study I we also found a older average LOS and higher age, compared to published data.[63-67] This could be caused by a higher turnover of PICU and AICU beds due to staff shortages, resulting in a pressure to discharge quickly. Age was obviously influenced by the fact that the youngest age groups (0-1 months in the PICU group and 0-6 months in the AICU group) were lacking in Study I. During this time, Sweden was 17th with regards to PICU beds per 100,000 inhabitants among the European countries.[68] Only five countries had fewer PICU beds per capita. The ICU admission rate of 1.59/1,000 children was slightly less than recent reports [63-66,69-70] but could be explained by the fact that the youngest children were not included in the cohort.

The survival curves from Study I and Study II display similar findings with regards to the diagnostic groups: miscellaneous had the poorest outcome, respiratory slowly continuously decreasing over the years' after PICU discharge, and post op and injury presented no or single number of fatalities. An important finding in Study I was that the study cohort had a 20-fold increase in yearly mortality compared to the reference Swedish population of the same age.

The data presented in Study I played an important role as a basis for discussion and judgement when the Swedish intensivists and professional societies met in 2013 and agreed on a national referral strategy: severely ill children should be transferred to a PICU as early as possible.[71] The reported number of children being transferred to PICU from AICU increased from 65 in Study I to 278 in Study II and to 601 from 2015 to 2017.[16, 17, 72] The Swedish need for intensive care for children seem to slowly increase over the last 20-years. Since the Swedish population did increase from 8.8 million in 1999 to 10.2 million in 2018,[73] there could be a true increase in numbers of PICU admissions in relation to this increased population.

Multiple admissions (MADM) and complex chronic conditions (CCC)

Through collected PIM2 data, in Study II we could confirm that Swedish PICU mortality was on par with published international data,[74] and the same decrease in survival over time post PICU discharge was seen as in Study I (*Fig 2-4 Study II*). The PIM2 score had not yet been fully implemented into the Swedish AICU routines, so we could only focus on the PICU population. Both MADM[75-77] and CCC[58] had previously been associated with increased PICU mortality. We wanted to explore these factors' impact on long-term outcome. An important and original finding presented in Study II was that not only where MADM and CCC associated with poorer outcomes post PICU discharge. Likewise diagnostic groups presented very different mortality rate ratios (MRR) concerning long-term outcomes. The impact of having a single admission (SADM), compared to multiple admissions (MADM) in combination with CCC resulted in differences in MRR from zero to seven times higher, depending on the admission diagnosis group. (*Table 3 Study II*). Multiple hospital admissions have been shown in a retrospective cohort[78] to be the most strongly associated factor with increased one-year mortality post hospital discharge. However, the presented cohort of 700,000 children under 21 years of age included no observations of PICU care but suggested that MADM could be associated with poor long-term survival.

Early (<48h) vs late (>48h) readmissions have been extensively discussed in the literature as a possible marker of quality of care.[75-77, 79-81] In Study II, we mainly focused on timeframes beyond this point but data on early and late readmissions are presented in table 10. The concept of chronic critical illness (CCI), (defined as length of stay >28 days in PICU), has also attracted some attention,[82] but under 2% of the patients in the cohort of Study II met the criteria. Therefore, we chose not to explore these data further.

PIM2 and arterial blood gas samples

To describe PIM2 was a key part of the data set of Study II. During the evaluation process we were criticized by some reviewers and editors since in the cohort "only" 55% of the admissions could demonstrate PIM2 with an arterial blood gas. If this was because PIM2 requires an arterial blood gas to be complete, we beg to differ. When PIM2 was first launched, only approximately 39% of admissions had an arterial blood gas included.[83]

Thus, we set out to investigate (I) whether an arterial blood gas only is needed if clinically demanded, and (II) in which diagnostic group it is needed to maintain accuracy of mortality prediction. To perform an arterial blood gas, the clinician often must inflict pain to the patient, and the process can be technically very difficult or even impossible in the acute care setting. We demonstrated that this step is only needed if clinically indicated and in patients belonging to the respiratory admission diagnosis group. With this information we pose that no unnecessary arterial punctures should be performed on PICU admission, and a PIM2 (or PIM3) dataset can be evaluated for accuracy according to how many of the patients with respiratory admission diagnosis had an arterial blood gas performed.

Limitation of medical treatment (LOMT)

In Study II, we found that many of the children died outside the PICU after discharge. This bothered us. To determine if LOMT was the factor limiting PICU readmission when the children turned fatally ill, we designed a novel study addressing this question. We analyzed the deceased children from the Study II cohort according to place of death after discharge: in the PICU, in a hospital, or at home. Of the children who died within one to four years after being discharged from PICU, 46% died without being readmitted to PICU. Both the hospital group (66%) and the home group (34%) had 75% LOMT, which represents only a minimal numeral, as there may have been LOMTs decided at the bedside that were not noted into the patients medical record. Further, it could be argued that the concept of LOMT could be used to withhold PICU care from children. The present Swedish trend, on the contrary, is to give children the benefit of doubt when possible. In addition there are long-term PICUs (so called LIVAs) for children in need of home-ventilator or other semi-chronic technical support. For example, children with severe neurologic conditions, including a low degree of perceived awareness, often have a very poor or lack of ability to cough and swallow (e.g. in scoliosis that restricts lung function). This group of patients represents an example where ethical questions can be a big challenge for both the physician and the family. Should the patient have ventilatory support, tracheostomy, and LIVA care for the rest of his/her life? The context of religion, cultural traditions and relatives involved can make these situations very difficult to manage. We perceive from our colleagues in Catholic European countries and from personal experience, that LOMT is often not a viable option and the end of a life in the PICU repeatedly involve legal conflicts.

It is worth reflecting on our finding that 75% of the children who die outside the PICU after discharge have a LOMT. Perhaps this should be 100%? According to the ethical codes suggested by the main textbook in Swedish intensive care,[3] intensive care should only be considered or performed if it can help the patient and cause no prolonged harm. If not, it should be withdrawn or not installed.

The present findings come with some limitations

In Study I, we did not have data on PIM2. In Study II, the children treated in AICU could not be focused on due to a lack of PIM2 data. The data evaluated originate from a single European country only (Sweden), which makes it problematic to judge external validity. If the database was 10 times larger, more precise conclusions could have been made. At present, some patient groups were small, and the presence of no or few individuals made statistical considerations problematic. However, this is an in-depth description and exploration of intensive care of Swedish children, so the narrow focus fulfills an initial goal of this thesis.

There are some strength to this data

We formed two separate cohorts of all Swedish children admitted to PICU care with only 5% lost to follow-up. The follow-up of the included children is close to 100%, thanks to the Swedish File of National Registration, which allowed us to collect mortality data on every deceased citizen. The two cohorts have been compared and were formed before and after a change in ICU-transfer policy. When first published, these data were unique and represented a basis for discussions regarding national policy changes.[68]

The presence of a sufficient number of available PICU beds is important, but even more important is the fact that the beds need to be staffed. Otherwise, the number of beds just represents a theoretical maximum capacity.

PICU care is a complex system that demands full attention. According to the document by the Swedish association of paediatric anaesthesia and paediatric intensive care, the "Svensk förening för barnanestesi och barnintensivvård" (SFBABI),[68] multiple admissions or readmission is a relative indication of transfer to PICU. Given the huge difference in MRR for different diagnostic groups some of the groups might always be considered for transfer. Some children at a certain stage of illness, where PICU care cannot affect the situation significantly, might eventually be more effectively managed in their local hospital. These decisions are delicate, and sound judgement by the clinician responsible at the bedside is of supreme importance.

7 CONCLUSIONS

1. Over the three years of the study (study 1, data 1998-2001) more than 8,000 admissions were made by more than 6,600 children to Swedish intensive care. A large number (56%) of the children admitted to ICU receive care in an adult ICU (AICU).

2. The Swedish PICU mortality and AICU mortality for these children were 2.5% and 1.9% respectively.

3. The long-term mortality (5-year) for the cohort was 7.3% (PICU) and 4.3% (AICU) respectively. There was an increased mortality (20 fold compared to the background population) for the whole cohort 5 years after discharge from PICU, although postoperative and injury patients showed no increase.

4. Swedish PICU care (study 2, cohort and data 2008-2010 with more than 5,000 admissions by 3,688 children) was on par with comparable countries and published outcome data.

5. Children with multiple admissions (MADM) and complex chronic conditions (CCC) did significantly worse over time post PICU discharge, particularly in cases of both MADM and CCC (study 2). Different admission diagnostic groups carry very different increases in mortality risk after PICU discharge, spanning from 0- to 7-fold increase in mortality risk ratio (MRR).

6. The ABG for PIM2 score should only be taken when clinically indicated or in children belonging to the respiratory admission diagnostic group.

7. The children discharged from PICU, who were not readmitted when lethally ill, had a LOMT limiting PICU readmission in 75% of cases at the time of death.

8 FUTURE PERSPECTIVES

On long-term outcome

Long-term outcome could and should be further explored. That would require a more detailed data set reported to SIR. However, the ICD10 diagnosis that are acceptable to SIR need to be more developed and diverse to be able to more precise describe diagnoses in the pediatric population. The chosen ICD10 diagnosis could then automatically render an ANZPIC grouping at discharge confirmed by discharging clinician. Of note, still close to 50 % of children in need of ICU care in Sweden are treated in an adult ICU. Therefore, all adult ICUs should be encouraged to report PIM3 score for all admitted children. Sweden has an advantage with the Cause of Death Register run by the National Board of Health and Welfare in Sweden, where long-term mortality can be assessed with very few patients lost-to-follow-up.

It would be desirable to better understand which children should be centralized and which groups could safely remain having their treatment in an adult ICU. As Sweden is a large country with a vast and sparsely populated northern section, it is unlikely that PICU care will be made available everywhere. Transporting unstable patients over a long distance also add risks, which have to be taken into consideration. Consequently, the manifold issues related to centralization versus 'stay-and-play' will continue and need further work and study.

On reserve identification numbers

Some patients, who arrives through the emergency, are initially unidentified and will receive a "reserve identification number", both physically (a plastic id-tag around the ankle) and noted into the medical journal. This number is generated locally at the admission hospital. Once the person is identified, the correct Swedish personal number will be used in the patients' medical journal. Consequently, two journals with two different identification numbers are created concerning the same patient. This obviously causes problems and insecurity at the actual care event, then again when a follow-up is planned. A more rational and secure way to do this would be if the reserve identification number were to be generated in one central computer, linked to the correct Swedish personal number. The patient would then have only one medical journal. This would certainly facilitate retrospective research and follow-up if organized on a national level for patient records.

On mortality outcome monitoring

Mortality outcome monitoring (and PIM3) etc. can be supplemented by level of "intact discharge". Thus, a parameter attempting to quantify morbidity at PICU discharge. It can be used to differentiate between children at risk for further problems and the risk of

death. Average level of morbidity measured on the discharged PICU patients need to be put in relation to the case mix in the PICU before evaluation is performed. Such a parameter has been used in congenital diaphragmatic hernia patients to evaluate the result of surgery and PICU care.[84-85] It adds another quality to discharge monitoring than just an ICD10 diagnosis.

On further exploration on the database

The database that was created for the second study contains a lot more than what has so far been published. Many different perspectives should be explored, such as need for hospital care post ICU discharge, quality of life evaluations, school performance, and more.

9 ACKNOWLEDGEMENTS

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EPILOGUE