Association of Nurse-to-Patient Ratios in the First 72 Hours of Admission and Outcomes of Very Preterm Infants: A Multicentre Cohort Study

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Abstract

Background: Very preterm infants born at <33 weeks Gestational Age (GA) are at high risk of short- and long-term complications. Neonatal Intensive Care Unit (NICU) organizational factors such as Nurse-to-Patient Ratios (NPRs) may contribute to patient outcomes. This study aimed to assess the association of NPRs received in the first 72 hours of admission with mortality and/or major morbidity among very preterm infants born <33 weeks GA.

Methods: This was a multicentre cohort study of inborn infants <33 weeks in 14 Level 3 NICUs in Canada between January 2020 and December 2021. Data on infant characteristics, NPRs and outcomes were obtained from the Canadian Neonatal Network database. NPR was recorded for the shift of admission, and a mean NPR was calculated for the first 24 hours, and first 72 hours of admission. Analysis was stratified by GA group to account for the differences in recommended NPR which are GA based (<29 and 29-32 weeks). Primary outcome was mortality and/or major morbidity. Three multivariable logistic regression models were fitted to estimate odds ratios adjusted for patient covariates with Generalized Estimating Equations to account for clustering within each site.

Results: The rate of mortality/major morbidity was 66% (633/952) among infants <29 weeks, and 19% (280/1501) among infants 29-32 weeks. The median NPR (Interquartile Range [IQR]) on shift of admission, first 24 hours, and first 72 hours were 1.00 [IQR 1.00-1.00], 1.00 [IQR 0.50-1.00], and 0.83 [IQR 0.53-1.00] for infants <29 weeks, and were 0.50 [IQR 0.50-0.50], 0.50 [IQR 0.50-0.75], and 0.50 IQR [0.50-0.58] for infants 29-32 weeks. In <29 week infants, there was insufficient precision and no evidence of an effect between higher NPRs received on the shift of admission (adjusted Odds Ratio (aOR); 0.63, 95% Confidence Interval (CI) 0.34-1.18), in the first 24 hours (aOR; 0.74, 95% CI 0.25-2.22), and in the first 72 hours (aOR; 0.82, 95% CI 0.24-2.76) of admission with mortality and/or major morbidity. Among infants born 29-32 weeks, higher NPR in the first 24 (aOR; 2.18, 95% CI 1.06-4.45) and 72 hours (aOR; 6.07, 95% CI 3.08-11.96) of admission were associated with higher odds of mortality and/or major morbidity.

Conclusion: Among infants born 29-32 weeks, higher NPRs in the first 24 and 72 hours of admission were associated with worse outcomes, which likely highlights confounding by indication as sicker infants are more likely to receive higher NPRs. In the <29 week infants, we were unable to estimate a precise association between higher NPRs and mortality and/or major morbidity. Further intervention studies are required to evaluate if active interventions to improve NPRs and organizational care are associated with outcomes in the NICU.

Keywords: Neonatal intensive care unit, Nurse-to-patient ratio, Preterm infant

Résumé

Contexte : Les grands prématurés nés à <33 semaines d'âge gestationnel (AG) présentent un risque élevé de complications à court et à long terme. Les facteurs organisationnels des unités de soins intensifs néonatals (USIN), tels que les ratios infirmières-patients (RIP), peuvent contribuer à l'évolution de l'état des patients. Cette étude visait à évaluer l'association entre les RIP reçus dans les 72 premières heures de l'admission et la mortalité et/ou la morbidité majeure chez les grands prématurés nés à <33 semaines d'AG.

Méthodes : Il s'agissait d'une étude de cohorte multicentrique portant sur des enfants nés <33 semaines dans 14 USIN de niveau 3 au Canada entre janvier 2020 et décembre 2021. Les données sur les caractéristiques des enfants, les RIP et les résultats ont été obtenues à partir de la base de données du Réseau néonatal canadien. La RIP a été enregistrée pour le quart d'admission, et une RIP moyenne a été calculée pour les 24 premières heures et les 72 premières heures de l'admission. L'analyse a été stratifiée par groupe d'AG pour tenir compte des différences entre les RIP recommandés en fonction de l'AG (<29 et 29-32 semaines). Le résultat principal était la mortalité et/ou la morbidité majeure. Trois modèles de régression logistique multivariables ont été ajustés pour estimer les rapports de cotes ajustés pour les covariables des patients avec des équations d'estimation généralisées pour tenir compte du regroupement au sein de chaque site.

Résultats : Le taux de mortalité/morbidité majeure était de 66 % (633/952) chez les enfants nés à <29 semaines et de 19 % (280/1501) chez les enfants nés de 29 à 32 semaines. La médiane de la RIP (écart interquartile [IQR]) au moment de l'admission, dans les 24 premières heures et dans les 72 premières heures était de 1,00 [IQR 1,00-1,00], 1,00 [IQR 0,50-1,00] et 0,83 [IQR 0,53-1,00] pour les enfants nés à <29 semaines, et de 0,50 [IQR 0,50-0,50], 0,50 [IQR 0,50-0,75] et 0,50 IQR [0,50-0,58] pour les enfants nés de 29 à 32 semaines. Chez les enfants nés à <29 semaines, il y avait une précision insuffisante et aucune preuve d'un effet entre des RIP plus élevés reçus lors de l'admission (rapport de cotes ajusté [RCA] ; 0,63, intervalle de confiance (IC) de 95% 0,34-1,18), dans les 24 premières heures (RCA; 0,74, IC de 95 % 0,25-2,22) et dans les 72 premières heures (RCA ; 0,82, IC de 95 % 0,24-2,76) de l'admission avec la mortalité et/ou de morbidité majeure. Chez les enfants nés de 29 et 32 semaines, une RIP plus élevée dans les 24 premières heures (aOR ; 2,18, IC de 95 % 1,06-4,45) et 72 heures (aOR ; 6,07, IC de 95 % 3,08-11,96) de l'admission a été associée à des probabilités plus élevées de mortalité et/ou morbidité majeure.

Conclusion : Parmi les enfants nés de 29 et 32 semaines, des RIP plus élevés au cours des premières 24 et 72 heures d'admission étaient associés à des résultats plus défavorables, ce qui souligne probablement la confusion par indication, car les enfants plus malades sont plus susceptibles de recevoir des RIP plus élevés. Chez les enfants nés à <29 semaines, nous n'avons pas pu estimer une association précise entre des RIP plus élevés et la mortalité et/ou la morbidité majeure. Des études d'intervention supplémentaires sont nécessaires pour évaluer si des interventions actives visant à améliorer les RIP et les soins organisationnels sont associées à des résultats en unité de soins intensifs néonatals.

Mots-clés : Unité de soins intensifs néonatals, Ratio infirmière-patients, Prématuré

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Contribution of Authors, Co-Authors, and Collaborators

The article presented in this thesis is titled "Association of Nurse-to-Patient Ratios in the First 72 Hours of Admission and Outcomes of Very Preterm Infants: A Multicentre Cohort Study" The initial study design for this project was founded by Dr. Marc Beltempo with input from collaborators. Co-authors participated in various stages of the project, including research ethics board submission, site coordination, critical review of the proposal, and manuscript. For the proposed article, Sabah Pirwani wrote the article as lead author under the supervision of Dr. Marc Beltempo and participated in all stages of the project. She drafted the research protocol and submitted the protocol to the Canadian Neonatal Network Ethics Committee. Data management and data analysis was conducted by Eugene Woojin Yoon, a biostatistician at the Canadian Neonatal Network Coordinating Centre located at the Maternal-Infant Care Research Centre in Toronto, Ontario. Sabah drafted the first version of the manuscript, modified it according to the co-authors' comments and is in the process of receiving and integrating final comments from all co-authors for submission to Pediatrics. Please note that the article presented in this thesis is not the final version that will be submitted for publication.

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List of Abbreviations and Acronyms

AAP	*American Academy of Pediatrics*
aOR	*Adjusted Odds Ratio*
BPD	*Bronchopulmonary Dysplasia*
BW	*Birth Weight*
BAPM	*British Association of Perinatal Medicine*
CI	*Confidence Interval*
CNN	*Canadian Neonatal Network*
FICare	*Family-Integrated Care*
GA	*Gestational Age*
GEE	*Generalized Estimating Equations*
IVH	*Intraventricular Hemorrhage*
IQR	*Interquartile Range*
MiCare	*Maternal-Infant Care Research Centre*
NEC	*Necrotizing Enterocolitis*
NI	*Nosocomial Infection*
NICU	*Neonatal Intensive Care Unit*
NPR	*Nurse-to-Patient Ratio*
OR	*Odd Ratio*
PVL	*Periventricular Leukomalacia*
ROP	*Retinopathy of Prematurity*
SGA	*Small for Gestational Age*
SNAP-II	*Score for Neonatal Acute Physiology, Version II*
SNI	*Severe Neurological Injury*
WANNNT	*Winnipeg Assessment of Neonatal Nursing Needs Tool*

Introduction

Each year, more than 4000 infants are born very preterm (<33 weeks' Gestational Age [GA]) in Canada and are admitted to one of 32 Neonatal Intensive Care Units (NICU) for specialized care.[1] Over 35% of those infants will either die or develop a major neonatal morbidity during initial hospitalization.[1] Importantly, very preterm infants account for more than 60% of costs for neonatal care in Canada and improving their outcomes is a public health priority.[2]

The availability of resources, specifically nursing staff, is critical for addressing the evolving and complex healthcare needs of these vulnerable infants. Adequate nurse staffing in the NICU allows for active monitoring, delivery of timely interventions, and individualized care. This ensures the provision of safe and effective patient care while optimizing health outcomes. Several early interventions (in the first seven days of NICU admission) have been associated with better outcomes in very preterm infants: maintaining normothermia on admission, early initiation of feeds and non-invasive ventilation success.[1,2,3,] NPRs may influence the ability to provide such interventions and subsequently affect infant outcomes. Previous studies have also suggested that lower NPRs are associated with a higher risk of improper hygiene practices, medical incidents, and increased missed care which can influence neonatal outcomes.[4,5,6,7]

Moreover, the majority of previous studies have evaluated NPRs at the unit-level by calculating the total number of nurses working (using specific guidelines) divided by the recommended number of nurses for a given time period. [5,8,9] Few studies have evaluated NPRs received by patients and their association with neonatal outcomes in the NICU.[10,11,12] Consequently, there is a need to evaluate if and how NPRs received by very preterm infants are associated with outcomes to optimize patient care and better allocate resources within the NICU.[11] Therefore, in this thesis, we will examine the association between NPRs in the first 72 hours of NICU admission and mortality and/or major morbidity among very preterm infants.

Chapter 1 – Literature Review

1.1 Neonatal Intensive Care Units

1.1.1 Classification of Neonatal Intensive Care Units

NICUs provide care to infants born preterm that require specialized care upon birth. NICUs are classified according to the level of care they provide.[13] In Canada, NICUs are classified as Level 1, 2 or 3. Level 1 NICUs provide care to healthy newborns and are usually located in general hospitals. Level 2 NICUs provide intermediate care to moderately ill infants with less complex health issues. Level 3 NICUs, often associated with university centers, provide specialized and intensive care, including interventions such as intubation and ventilation, for critically ill infants of any GA. There are 32 Level 3 NICUs in Canada.[14]

When a mother is at risk of imminent preterm delivery, they are ideally transferred to a hospital with a Level 3 NICU where a specialized team can stabilize the neonate immediately after delivery. Conversely, in the event of an unplanned delivery of a high-risk newborn in a hospital with a Level 1 or 2 unit, the local (and less experienced teams) are responsible for stabilizing the infant and coordinating their transfer to a Level 3 unit.

1.1.2 Organizational Care Structure

The analysis of care structure in the NICU can be stratified into two systems, as proposed by Nelson: the mesosystem and the microsystem.[15] Each system is characterized by distinct goals and organizational structure.[16] The mesosystem involves the connections and interactions between the different microsystems. In the NICU, this can include the interactions between healthcare providers, nursing staff, and family members. The microsystem refers to the infants' direct interactions within the NICU. This encompasses the activities that directly impact the patient and the resources specifically allocated to each patient during hospitalization. Organizational variables within these systems may impact infant outcomes, thus it is important to better understand how optimal resource allocation in the NICU can improve infant outcomes. In this study we will be assessing the impact of resource allocation in the microsystem, specifically the NPRs that infants directly receive, on neonatal outcomes.

1.1.3 Cost of Neonatal Care

In 2022, over 15,000 infants were admitted to one of 32 Level 3 NICUs in Canada.[14] Importantly, the cost of neonatal care for preterm infants is significant. A study conducted by Rios et al. found that NICU costs for preterm infants admitted to 30 Level 3 NICUs in Canada increased as gestation decreased and length of stay increased. The median (interquartile range [IQR]) cost for NICU care was estimated as $30,572 ($16,597-$51,857) with a mean length of stay of 28 days for 29-32 weeks infants; and $100,423 ($56,800-$159,358) with a mean length of stay of 66 days for <29 weeks infants.[17]

In the United States, 27% of the overall budget of pediatric hospitals is designated for the treatment of premature and low-birth-weight infants.[18] In Canada, neonatal units incur the second-highest average cost per day of hospitalization among specialized pediatric care units, varying from $1139 to $1890.[19] These units also record the longest average duration of hospitalization at 13.9 days.[19]

1.1.4 Donabedian Triad

The Donabedian triad is a methodological framework for evaluating health services and the quality of care. This model includes three key dimensions: structure, process, and outcomes **(Figure 1)**.[20,21]

1. Structure pertains to the environment or setting in which care is provided. It includes all resources needed for the provision of care, such as material resources (hospital building, equipment), intellectual resources (information systems) and human resources (staff).
2. Processes refer to the activities and interactions between patients and healthcare providers during the delivery of care. It encompasses the interventions occurring throughout the provision of care, such as treatments and medications administered and hand washing.

3. Outcomes relate to the impact of the interaction between the structure and processes. Outcomes can be organized into three categories that have corresponding outcome indicators: patient-focused (health status, patient satisfaction, patient knowledge), provider-focused (fatigue, job satisfaction) or organization-focused (healthcare costs, length of stay).[22]

Figure 1. Donabedian's framework for evaluating health services

Overall, the Donabedian triad highlights that the structure of care and care processes to which patients are exposed may contribute to health outcomes. It is therefore essential to assess how organizational variables in the NICU contribute to outcomes of very preterm infants.

1.2 Prematurity

1.2.1 Definition

Preterm birth is defined as birth before 37 weeks GA.[17] According to the World Health Organization, there are three sub-categories of prematurity: extreme preterm, which includes infants born at <28 weeks of gestation; very preterm, which includes infants born between 28 to 32 weeks of gestation; and moderate to late preterm, which includes infants born between 32 to 37 weeks gestation.[23] It is important to note that sub-categories of prematurity vary between the World Health Organization and the CNN. The CNN defines extremely preterm infants as those born at <29 weeks gestation, very preterm infants include infants born at <33 weeks gestation, and preterm infants include those born at <37 weeks gestation. As the study is based on data acquired from the CNN database, the CNN definition of very preterm will be applied for the purpose of this study.

In preterm infants, weight usually increases with gestational age.[24] Low birth weight includes infants that weigh <2500 grams, very low birth weight is defined as <1500 grams and extremely low birth weight includes infants that weigh <1000 grams.

1.2.2 Incidence and Cause of Prematurity

Preterm birth is the leading cause of infant death and disability in Canada.[2,25] Approximately 8% of pregnancies result in preterm birth in Canada.[2] In 2021, this represented 29,208 births.[26]

There are two main causes of preterm birth: spontaneous preterm delivery and indicated preterm delivery. Spontaneous preterm delivery refers to the onset of labour and subsequent delivery without medical indication,[27] whereas indicated preterm delivery refers to delivery for maternal or fetal indications and occurs when labour is induced or the infant is delivered by a cesarean section to reduce the risk of maternal or fetal complications. [23,28] In most cases the specific cause of the spontaneous preterm birth is unknown, however, it can be attributed to multiple factors such as infection, environmental, sociodemographic, and genetic factors.[29,28] Common causes of indicated preterm birth can include pre-eclampsia and intrauterine growth restriction.[28]

1.2.3 Complications of Prematurity

Infants born before 37 weeks' gestation are at a higher risk of neonatal mortality or short and long-term morbidities and thus require specialized care.[30] The literature has revealed that survival in preterm infants tends to increase with increasing gestational age, therefore risk of death and morbidities is inversely related to GA.[1,31] Among preterm infants, the group of infants born <33 weeks GA are at highest risk of death and morbidities, hence their admission in specialized units.

Important morbidities in very preterm infants include Bronchopulmonary Dysplasia (BPD), Nosocomial Infection (NI), Necrotizing Enterocolitis (NEC), Severe Neurological Injury (SNI), and Severe Retinopathy of Prematurity (ROP). These major morbidities are used as markers of quality of care by the majority of neonatal outcomes research, and have standardized and internationally recognized definitions as they are associated with the medium and long-term outcomes of the infant.[32,33]

1.2.4 Bronchopulmonary Dysplasia

BPD is a chronic lung disease that primarily affects preterm infants. It is defined as requirement for supplemental oxygen or respiratory support at 36 weeks corrected GA (adjusted age accounting for the time infant was born before reaching term) due to respiratory distress.[34,35] BPD is the most common complication of prematurity and more than 50% of infants born <29 weeks GA will either die or develop BPD.[34,35] Infants born at an earlier GA and that have a lower Birth Weight (BW) are at the highest risk of developing this complication. BPD can be attributed to multiple causes such as a surfactant deficiency, persistent inflammation, prolonged invasive ventilation, and oxidative damage.[36,37] It has been associated with various risk factors such as an increased risk of childhood mortality, long-term respiratory complications, growth failures, feeding difficulties, pulmonary hypertension and neurodevelopmental impairment.[34,38,39,3]

1.2.5 Nosocomial Infection

NI, also referred to as healthcare-associated or healthcare-acquired infections, is defined as infections acquired during the period of hospitalization. Neonatal sepsis can be classified as early-onset sepsis (<72 hours after birth) or late-onset sepsis (>72 hours after birth).[40] Early-onset sepsis is an infection acquired from the mother in utero or during delivery (passage through the birth canal).[41] Late-onset sepsis is an infection that is acquired during hospitalization and the postnatal environment with the majority of infections occurring in the first 40 days following birth.[41,42] When reporting NI rates in very preterm infants, the majority of neonatal networks define it as a positive blood and/or cerebrospinal culture in a symptomatic infant.[43] The term NI encompasses a range of infections which include bloodstream infections, meningitis, central-line infections, bacteremia, viral infections, etc.[44] The majority of neonatal networks do not include ventilatory-acquired pneumonia, urinary tract infections and surgical site infections due the absence of consensus definitions for those type of infections in preterm infants.[45] NI can be caused by bacteria, viruses, and/or fungi.[44] Infants admitted to the NICU are at an increased risk of acquiring NIs which ultimately leads to increased morbidity, mortality, and prolonged lengths of stay in the hospital.[43,46] NIs affect 5% of all newborns admitted to NICUs, and this proportion increases to 10% in very preterm infants born <33 weeks GA.[42] Risk factors for NI include low gestational age, low BW, mechanical ventilation, venipuncture, incidence of asphyxia, feeding intolerance, central lines, inadequate nursing ratios, NICU overcrowding, and exposure to broad-spectrum antibiotic.[44,46,47,48] The most common form of NI within the NICU is a catheter-associated bloodstream infection (bacteremia) which can be due to ongoing care of the catheter site in combination with the inherent risk of having foreign devices in vulnerable patients.[46,47] Bacteremia, which is a systematic infection, is associated with long-term morbidity, mortality, and increased healthcare costs.[42] One of the main prevention practices to minimize the risk of nosocomial infections includes proper hand hygiene and handwashing, as many types of pathogens can be transmitted by the hands of healthcare professionals.[42,49]

1.2.6 Necrotizing Enterocolitis

NEC is a severe intestinal inflammatory disease with 90% of all cases occurring in preterm infants, and thus a major cause of morbidity and mortality in the NICU.[50,51,52] The frequency of NEC in preterm infants is inversely related to BW,[52,53] and as a result the majority of cases are detected in infants born <33 weeks GA.[54] Despite decades of extensive research, the etiology remains unclear and is believed to be multifactorial.[51] Introduced in 1978 and subsequently modified by Kliegman and Walsh, Bell's staging classifies the severity of NEC in three stages and provides guidance for treatment approach.[53] Risk factors for NEC include immaturity of the gastrointestinal tract regarding motility, digestive function, circulatory regulation, barrier function, and immune defense.[55] A systematic review and meta-analysis published in 2020, reported that 7 of out 100 infants admitted to the NICU that are very low birth weight (BW < 1500g) are likely to develop NEC.[56]

1.2.7 Severe Neurological Injury

SNI is defined as Intraventricular Hemorrhage (IVH) grade 3 or greater and/or Periventricular Leukomalacia (PVL), which are the two main types of SNI in preterm infants.[57] SNI is a major cause of long-term neurodevelopment impairments in preterm infants. Risk factors for SNI in very preterm infants include low GA, low BW, mechanical ventilation, use of vasopressors, and birth outside a tertiary care centre.[57,58,59]

PVL is an ischemic lesion of white matter in the periventricular area of the brain and is commonly seen in premature infants.[60] It is often a result of insufficient blood flow or oxygen to this area. IVH is characterized by bleeding into the ventricles of the brain.[61] The severity of IVH is assessed according to the Papile grading system, which includes 4 categories.[62] The severity of hemorrhage is based on the extent of bleeding, parenchymal involvement, and the presence of ventricular distension.[58] Grade 1 IVH is limited to the germinal matrix; Grade 2 IVH involves bleeding into the ventricles without ventricular dilation; Grade 3 IVH involves bleeding into the ventricles with ventricular dilation; Grade 4 IVH refers to intraventricular bleeding with intraparenchymal hemorrhage.[63] Grades 1 and 2 IVH are considered to be low grade, whereas Grades 3 and 4 are considered severe.

1.2.8 Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease affecting the retina of premature infants, where the retinal vascular development is incomplete.[64,65] Vascularization of the retina typically begins at 16 weeks GA and continues until the end of gestation, as such, premature infants are born with incompletely vascularized retinas.[66] ROP can be caused by multiple factors, however, the most common are low GA, low birth weight, and exposure to high levels of oxygen.[64,67] Long-term complications of ROP include myopia, muscular scarring, cataracts, glaucoma, and retinal detachment.[66]

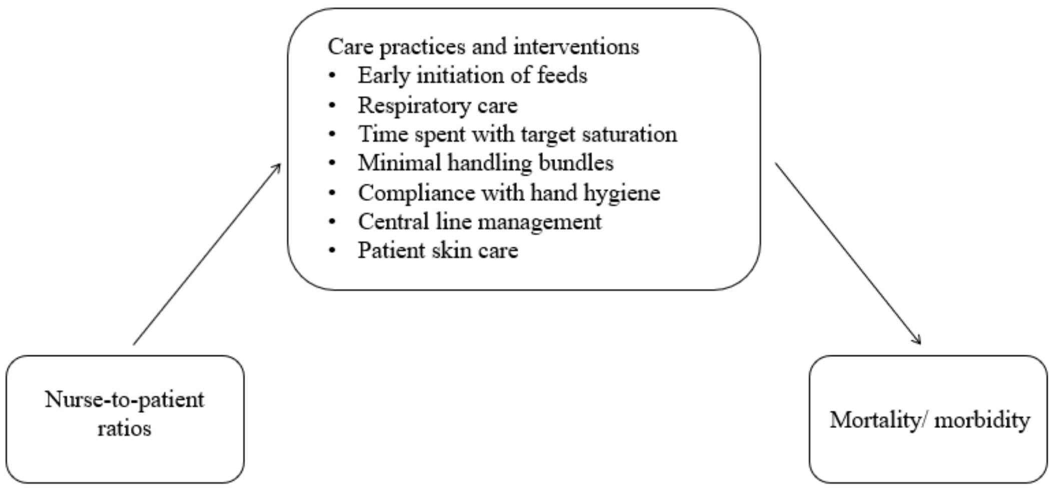
The abnormal vessel development in ROP occurs in two phases. Phase I, the vaso-obliteration phase, is characterized by delayed retinal vascular development and partial regression of existing vessels.[68] Phase II, the vaso-proliferative phase, is defined by the formation of new abnormal vessels associated with retinal hypoxia.[68,69]

ROP is classified according to the affected zone and the level of severity which is outlined by the International Classification of Retinopathy of Prematurity to guide management and treatment.[66] The stages range from mild (stage 1) to severe (stage 5), based on the extent of abnormal blood vessel growth and retinal detachment.[70] A study reported more than 40% of at-risk preterm infants develop some stage of ROP, and approximately 12.5% develop severe ROP, which is usually seen in infants with a BW of less than 1251 grams.[71]

1.2.9 Early Interventions and Care Practices

It is known that preterm infants are at a higher risk of neonatal morbidity and mortality compared to term infants.[30,72] The smaller the infant in terms of weight and GA, the higher the risk.[73] The first seven days of NICU admissions is considered a critical period for prevention of mortality and major morbidity in preterm infants, as most neonatal deaths occur in the first seven days of birth.[74,1] As such, the care practices and interventions provided at the time of birth and during these critical periods can have important effects on neonatal outcomes **(Figure 2)**.[30] More specifically, several early interventions have been associated with better outcomes in very preterm infants, such as maintaining normothermia on admission, minimal handling bundles, early initiation of feeds, and successful use of non-invasive ventilation.[1,3] Sink et al. conducted a study that aimed to assess the association between NPRs at the patient-level and the achievement of oxygen saturation goals in infants born <29 weeks gestation. The findings suggested that having fewer infants assigned to a nurse allows for more precise oxygen management which in turn may influence infant outcomes.[12] Moreover, having more infants assigned to a nurse may result in less time for individual care, thereby increasing the risk of certain adverse outcomes such as ROP or BPD.[12] The literature has also shown that the interventions and care practices received during the "golden hour" or the first 60 minutes of postnatal life can have important effects on short and long-term neonatal outcomes. Studies that have observed the golden hour have shown a reduction in long-term health outcomes such as IVH, BPD, and ROP.[75] This highlights the importance of having appropriate nurse staffing during critical periods to ensure that infants receive adequate care.

Figure 2. Mediating factors influencing the relationship between the nurse-to-patient ratios and neonatal outcomes



1.3 Nurse-to-Patient Ratios

1.3.1 Unit-Level vs. Patient-Level Analysis

Studies have used several approaches to assess the association between nurse staffing levels and infant outcomes. Some studies have analyzed the exposure from the individual patient's perspective, while others have analyzed the exposure from a unit perspective. Both approaches have methodological advantages and limitations according to the objective of the analysis.

At the unit-level, the exposure is observed from the unit's point of view, whereas the outcome is observed from the patient's point of view. For example, a study conducted by Beltempo et al. aimed to assess the association between nursing provision and unit occupancy with mortality and/or major morbidity among very preterm infants. Nursing provision was observed at the unit-level by calculating the total number of nursing hours worked divided by the total number of required nursing hours based on patient acuity categories.[9] A limitation of this methodology is that the ratio of total nurses per patient does not specify what the individual patient received, thus it is difficult to know whether a given patient who developed the outcome was actually exposed to, for example, a sub-optimal NPR. As this method relies on unit-level data, there could be the risk of ecological bias if group-level data is used to draw conclusions about individual-level relationships.[76]

At the patient-level, the exposure and the outcome are both observed from the patient's point of view. In other words, the patient-level analysis observes the association between the exposure, for example, the nurse-to-patient ratio that an infant receives and the patient's risk of developing a complication during a specified timeframe. Statistically, patient-level analysis allows the risk to be modelled and adjusted for each patient's exposure. This approach is useful for outcomes that occur only once per patient and have a consistent definition of exposure across all patients. For example, we can observe the association between the NPR assigned to an infant for a given time period and the risk of that patient developing neonatal outcomes. A limitation of this methodology is it does not account for organizational factors and fluctuations in nursing workload, as NPRs can vary throughout the shift or day. Consequently, an infant may be assigned a specific NPR, however, this assignment may not always be accurate, particularly when nurses cover for their colleagues during breaks. Overall, analysis based on the patient as the point of analysis provides a complimentary understanding of NPRs on the individual health outcomes of patients in the NICU.

1.3.2 Nurse-to-Patient Ratios and Patient Outcomes

Preterm infants require a significant level of care and resources and maintaining adequate NPR is a constant stressor in the majority of NICUs in high-income countries.[77] A number of factors are considered in order to assess the optimum level of NPRs required, such as patient acuity, the number of admissions, discharges, transfers during a shift, level of experience of nurses, and the availability of resources.[78] Studies conducted in both adult and infant populations have shown an association between nurse staffing levels and patient outcomes.

Studies have revealed that higher NPRs are associated with increased mortality and adverse outcomes in adult intensive care unit. [79,80,31] Needleman and al. published a study in 2002 on the effects of nursing time on patient outcomes. They analyzed administrative data from 799 hospital in the United States and found an association between higher proportion of total hours of nursing care and lower rates of adverse outcomes. In medical patients they found that higher levels of staffing by nurses was associated with a decrease in length of stay, rates of urinary tract infections and upper gastrointestinal bleeding.[79] In surgical patients they observed an association between higher levels of staffing by nurses and a decrease in rates of pneumonia, shock, and cardiac arrest.[79] The results highlight that more nursing care time was associated with higher overall quality of care delivered. Another study conducted by Needleman et al. revealed an association between increased patient mortality with increasing exposure to shifts in which total nurse hours were 8 hours or more below target staffing levels.[80]

Similarly, studies assessing nurse staffing levels in the NICU have shown comparable results. Watson et al., conducted a study that aimed to assess the effect of a one-to-one NPR on mortality rates in a Level 3 NICU.[81] Importantly, they found that decreases in the proportion of one-to-one nursing was associated with increased mortality rate in the NICU. Furthermore, a single-center retrospective cohort study published in 2003, aimed to assess the effect if infant to staff ratios in the first three days of life with mortality in very low birthweight infants. The findings showed a decline in risk-adjusted mortality associated with fewer nurses caring for high-risk infants (higher infant to staff ratio).[82] The authors suggested that one possible explanation for these findings is that when there are more nurses available, it may lead to increased handling of these high-risk and vulnerable infants which contribute to adverse outcomes for the infants.

A systematic review of studies published in 2013 noted that NPRs at the unit-level affected outcomes in the NICU.[8] Six studies were identified and suggested that NPRs are associated with a reduction in mortality and other adverse outcomes in the NICU. This relationship could not be confirmed by a meta-analysis due to the heterogeneity between the small number of studies published and the variation in definitions of NPRs used in each study.[8]

Overall, neonatal studies observing the relationship between NPRs and patient outcomes have shown mixed results, which may be in part due to the interaction of various NICU organizational factors.

1.3.3 Missed Care

The quality of care provided to infants during their hospitalization can have important effects on neonatal outcomes. Nursing workload, commonly defined as the amount of time needed to fulfill nursing responsibilities, is frequently assessed through resource-based metrics, such as patient acuity scores or categories with corresponding recommended nursing ratios.[4] Importantly, high nursing workload can result in missed care and in turn impact infant outcomes. The literature has shown an association between high nursing workload and reduced capacity to monitor patients.[80]

A study conducted by Tubbs-Cooley et al. aimed to evaluate the association of NICU nursing workload with missed care and found a significant association between lower NPRs (more infants per nurse) and increased odds of missed care.[4] Further, missed care events were reported to occur during 98.2% of all nursing shifts, and nurses most commonly reported missing hourly assessment of the intravenous site and adherence to central venous catheter infection prevention bundles.[4] Moreover, a study conducted in 2015 that observed missed care among NICU nurses suggested that missed care was associated with infant outcomes, including prolonged time to achieve full-feeding and increased length of stay.[83,84] Importantly, preterm infants represent a vulnerable population that requires continuous care, and missed nursing care can result in adverse patient outcomes.

1.3.4 Medical Accidents

Preterm infants require constant monitoring and specialized care and as a result are more vulnerable to medical accidents which can include medication errors, diagnostic-therapeutic errors or feeding and equipment failure.[43,85] A study conducted by Beltempo et al. examined the association of nursing overtime, nursing provision and unit occupancy rate with medical incident rates in the NICU and the risk of mortality or major morbidity among very preterm infants. In this study, medical accidents were defined as "observable errors in the process of care with or without direct consequences on the patient's health."[5] The results revealed that medical accidents occurred on days with lower median nursing provision ratios. The majority of medical accidents involved errors in medication administration or dosage, while others were related to feeding, treatments and procedures. This suggests inadequate staffing increases the risk of developing adverse outcomes and may be influenced by reduced adherence to practice guidelines.

1.3.5 Nursing Overtime

Overtime may be used to maintain staffing levels when there are changes in patient needs, such as unplanned admissions, patient mix, changing caseload[43] and unexpected staffing changes (sick calls, leave of absence).[86] This encompasses both voluntary or mandatory hours worked beyond a scheduled shift, additional hours beyond a scheduled 8 or 12-hour shift, or more than 37.5 hours per week.[87] Higher occupancy can increase nursing workload, prompting the use of nursing overtime to maintain adequate NPRs.[88,89] Nursing overtime has been associated with burnout and fatigue, which can in turn impact the quality of patient care.[43,90,91] In the adult population, the literature has shown an association between nursing overtime and medication errors, needlestick injuries, infections, and mortality.[92,93,94] However, neonatal studies on nursing overtime have shown mixed results which may be due to methodological differences in accounting for confounders, including organizational factors. A study aimed to examine the association of nursing overtime, nursing provision and unit occupancy rate with risk of mortality or major morbidity among very preterm infants did not find a relationship between nursing overtime and the composite outcome.[5] Further, another study showed an association between nursing overtime and higher odds of health care-associated infections in the NICU.[87] Overall, using overtime as a strategy to maintain NPRs in the NICU may contribute to staff burnout and fatigue, potentially impacting the quality of care infants receive.

1.3.6 Unit Occupancy

The literature presents mixed results on NICU occupancy rates with neonatal outcomes. A multicentre cohort study conducted by Beltempo et al. investigated the association between NICU nursing provision and unit occupancy (proportion of occupied beds) rate with outcomes of very preterm infants. The study found an association between higher NICU occupancy rates on the shift of admission and in the first 24 hours of admission with higher odds of mortality/morbidity. Importantly, higher occupancy rates in the NICU have been associated with higher nursing workload, however, the authors found that nursing managers are adjusting the number of nurses based on patient acuity which may reduce the effect of occupancy.[9]

Similarly, Tucker et al. conducted a multicentre study of 13,515 infants admitted to 186 NICUs in the United Kingdom. They evaluated the impact of occupancy rate, NPRs, and workload on neonatal outcomes. The findings revealed that the risk of in-hospital mortality increased when the patient was admitted to a unit with a high occupancy rate.[95]

Conversely, a large population-based study in Canada, that included 23 neonatal units and 9978 newborns aimed to assess the association between occupancy rate in neonatal units at admission and the risk of mortality and morbidity in newborns. The results showed no association between occupancy rate and the risk of morbidity and mortality.[96] Overall, these mixed results can be attributed to the complex interaction of various organizational factors within the NICU, affecting neonatal outcomes.

1.3.7 Risk Adjustment

In neonatal studies, risk adjustment involves accounting for factors that may influence outcomes in infants, enabling comparison among different patient populations. We can account for these confounding factors by adjusting for these variables in our statistical analysis.

Patient acuity is a clinical indicator used to assess the severity and complexity of a patient's condition, considering factors such as medical needs, interventions, and monitoring requirements.[97] In the context of the NICU, patient acuity tools can be used to categorize infants according to the severity of their condition and predict the associated risk of morbidity and mortality, which is a method that allows nursing managers to allocate resources.

The Score for Neonatal Physiology (SNAP) is an instrument widely used in neonatology to assess the severity of illness in infants and compare outcomes across different NICUs.[98] The tool has evolved over time, with different versions developed to enhance its accuracy and relevance. The most widely used version is the Score for Neonatal Acute Physiology, version II (SNAP-II) which is a revised and validated version of the original SNAP tool. It is comprised of six components that are measured in the first 12 hours following birth, and the score ranges from 0 (low severity) to 115 (high severity).[98] An illness severity score of > 20 is generally associated with a higher risk of mortality.[72] In 2019, Beltempo et al. conducted a study where they aimed to re-validate the tool in infants born 22 to 28 weeks' gestation. More specifically, they wanted to determine SNAP-II cut-off scores associated with outcomes in extremely preterm infants, which included early and hospital mortality, mortality/morbidity, and individual morbidities (BPD, SNI, ROP, NEC and NI). The authors suggested a different threshold (ranging from 12 to 20) for each of these health outcomes, concluding that the SNAP-II score is an appropriate predictor of mortality and morbidity for these infants.[72]

1.3.8 Methods for Assessing Nursing Staffing Requirements

Various methods can be used to assess nursing staffing requirements in the NICU. Sawatzky-Dickson and Bodnaryk outlined five methods in a paper published in 2008:

1. Professional judgment: This approach relies on the expertise of unit professionals to decide the appropriate number of nurses required for each shift. Although this method is efficient, it is subjective as it relies on clinal experience and knowledge.
2. Nurse per occupied bed: This method uses formulas established through research studies to calculate the necessary number of full-time nurses in comparable units required for adequate care.
3. Acuity-quality: This approach categorizes patients based on health status and estimates nursing time required for each category. This approach allows for ongoing assessment of patient needs based on the number of patients in each category during a given shift.
4. Time-task/activity: This method involves assigning a specific number of minutes to each nursing task required for a given patient, with nurses calculating the cumulative requirements from individual care plans. This method has limited predictive value as estimating future patient care needs can be challenging.
5. Regression analysis: This approach predicts the necessary nursing staff required based on specific activity levels or number of patients.

1.4 Nursing Workload Assessment Tools

Nursing workload was defined in 1975 by Caplan & Jones as the quantity of tasks performed in order to carry out nursing activities in a specific period of time.[99] Later, Prescott et al. emphasized that nursing workload includes both direct and indirect care, where direct care includes all nursing activities carried out in the presence of the patient and/or family and indirect care accounts for any work carried out away from, but on behalf of, a specific patient.[99] Further, a literature review conducted in 2007 on the conceptualization of nursing workload highlighted that patient acuity should not be the sole consideration as a measure of nursing workload. It should also consider non-patient related nursing work, the complexity of care and skill mix (knowledge and experience required to provide a standard of care for a certain level of demand)[100] required to deliver adequate patient care.[99] Consequently nursing workload assessment tools are an acuity-quality approach to evaluating nursing needs in the NICU.

The utilization of nursing workload assessment tools by NICU managers is essential for assessing staffing requirements in the NICU. The use of standardized and validated tools is crucial to optimize both efficiency and the quality of care provided.[101] Specifically, the American Academy of Pediatrics (AAP), the Winnipeg Assessment of Neonatal Nursing Needs Tool (WANNNT), and the British Association of Perinatal Medicine Tool (BAPM) were developed for the purpose of determining the level of nursing care required by newborns in the NICU.

1.4.1 American Academy of Pediatrics

In 1992, the AAP tool was developed with the American College of Obstetricians and Gynecologists to establish nurse staffing guidelines. The tool includes five categories of patient acuity for neonatal intensive care with associated NPRs **(Table 1).**[77] The lowest patient acuity group is defined by “newborns requiring continuing care” and the highest patient acuity group is defined as “unstable newborns requiring complex and critical care”.

Table 1. American Academy of Pediatrics Tool

Category	Nurse-to-Patient Ratio
Newborns requiring continuing care	1:3-4
Newborns requiring intermediate care	1:2-3
Newborns requiring intensive care	1:1-2
Newborns requiring multisystem support	1:1
Unstable newborn requiring complex critical care	1:1 or greater

Table from Kilpatrick, S. J., Papile, L. A., & Macones, G. A. (2017). *Guidelines for perinatal care.* American Academy of Pediatrics.

A study conducted by Rogowski et al., that looked at nurse staffing of NICUs in the US, gathered a panel of experts, including a neonatologist, a perinatal nurse specialist and a representative of the National Association of Neonatal Nurses. The panel aimed to refine the five infant acuity categories initially outlined by the AAP and American College of Obstetricians and Gynecologists by incorporating specific infant characteristics **(Table 2)**.[77]

Table 2. Operational definitions of infant acuity levels originally described by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists

Infant Acuity Level	Original Description	Operational Definition	NPR
1	Continuing care	Infant only requiring oral or nasogastric feedings, occasional enteral medications, basic monitoring. May or may not have a heparin lock for meds.	0.25-0.3
2	Requiring intermediate care	Stable infant on established management plan, not requiring significant support. Examples would include: Room air, supplemental oxygen or low flow nasal cannula, several meds.	0.3-0.5
3	Requiring intensive care	Infant is stabilized, though requires frequent treatment and monitoring to assure maintenance of stability. Examples would include: Ventilator, CPAP, high-flow nasal cannula, multiple IV meds via central or peripheral line.	0.5-1
4	Requiring multi-system support	Infant requires continuous monitoring and interventions. Examples would include: Conventional ventilation, stable on high-frequency ventilation, continuous drug infusions, several IV fluid changes via central line.	1

5	Unstable, requiring complex critical care	Infant is medically unstable and vulnerable, requiring many simultaneous interventions. Examples would include: ECMO, high-frequency ventilation, nitric oxide, frequent administration of fluids, medication.	1 or >1

Abbreviations: CPAP, continuous positive airway pressure; IV, intravenous; ECMO, extracorporeal membrane oxygenation; NPR, nurse-patient ratio.

Table from Rogowski, J. A., Staiger, D. O., Patrick, T. E., Horbar, J. D., Kenny, M. J., & Lake, E. T. (2015). Nurse staffing in neonatal intensive care units in the United States. *Research in nursing & health*, 38(5), 333-341.

1.4.2 Winnipeg Assessment of Neonatal Nursing Needs Tool

The WANNNT is a tool that was developed by a Canadian research team as part of a study aimed at building and validating a tool for assessing nurses' workloads. The team of researchers implemented an acuity-quality approach to guide the development of the tool.[102] A group of nurses developed a set of indicators that gives guidance on patient acuity level and the nursing workload required. Levels of care were developed according to the grouped indicators that allowed for patients to be matched with the correct level of care. Each of the six patient levels is associated with a certain patient indicator as well as a recommended NPR.

A study conducted by Sawatzy-Dickson and Bodnarky aimed to test the validity and reliability of this nursing workload assessment tool. Nurses provided an estimation of care time for patients which was used to compare the nursing time assessment assigned by the WANNNT. The results showed that the difference between the number of nurses required estimated by the nursing workload assessment tool and the nurses’ estimation was statistically insignificant for levels 1-5. However, for level 6, nurses estimated 50% less time than the tool assigned. Overall, the tool provided a reliable estimation of nursing assignments for patients requiring different levels of care to provide the highest quality of care.

Table 3. Winnipeg Assessment of Neonatal Nurse Needs Tool

Patient Level	Patient Indicators	NPR
1	Postnatal care of healthy term newborn with or without phototherapy Peripheral IV to heplock with 2 or less piggyback meds (i.e. Antibiotics) Has met discharge criteria Healthy infant with significant social issues	0.25
2	Oxygen therapy and oximetry Cardio-respiratory monitoring Peripheral IV with 2 or less solutions Peripherally inserted central catheter (PICC)/ cutdown central venous line Total parenteral nutrition Uncomplicated gavage/breast/bottle feeds Uncomplicated chronic stable ostomy Neonatal abstinence scoring Convalescing infant with parents requiring teaching Hyperbilirubinemia with high potential for exchange transfusions	0.3
3	Stable Nasal CPAP or stable trach to CPAP Frequent cardio-respiratory events Umbilical venous line/ Epidural infusion > 24 hours Feeding: significant difficulty or intensive parent education (i.e. home tube feeding) Complicated ostomy care / appliance changes / complex skin care Unstable infant of diabetic mother with frequent blood glucose monitoring Cardiovascular or respiratory instability with handling Active neonatal withdrawal syndrome	0.5
4	Mechanical ventilation – stable with few changes and/or weaning Unstable Nasal CPAP potentially requiring intubation Frequent significant cardio-respiratory events Invasive pressure monitoring Stable blood pressure on one vasopressor with few changes Cardiac anomaly requiring Prostaglandin infusion Single chest tube Seizures Intensive oxygen management with >10 adjustments/hour	0.7
5	External ventricular drain requiring frequent adjustments Mechanical ventilation ETT or trach with unstable respiratory status requiring frequent blood gases and vent changes Nitric Oxide Hemodynamically variable with up to 2 inotropes Peritoneal or hemodialysis Multiple chest tubes Consistently high pain / agitation scores or intensive pain management End of life care / active advanced care planning	1
6	Hemodynamically extremely unstable requiring more than 2 inotropes or high doses with frequent changes, i.e >one change/hour	1.5

	Post-operative cardiac surgery (excluding PDA) for first 24 hours Extracorporeal membrane oxygenation Active disseminated intravascular coagulation with frequent blood products Continuous fluid boluses and changes

Abbreviations: NPR, nurse-patient ratio; IV, intravenous; CPAP, continuous positive airway pressure; ETT, endotracheal tube; NIRS, near infrared spectroscopy; aIEEG, amplitude-integrated electroencephalography; PDA, patent ductus arteriosus; CRRT, continuous renal replacement therapy

Table from Sawatzky-Dikson, Doris & Bodnaryk, K. (2009). Validation of a tool to measure neonatal nursing workload. *Journal of nursing management*, 17(1), 84-91.

1.4.3 British Association of Perinatal Medicine Tool

The Service Standards for Hospitals Providing Neonatal Care contains a tool that is used in the United Kingdom. This tool has three levels of patient care with corresponding guidance on the number of nurses required which was established based on professional consensus. [103]

Table 4. British Association of Perinatal Medicine Tool

Care Required	Description	Nurse-to-Patient Ratio
Intensive care	Due to the complex needs of both the baby and their family the ratio of neonatal nurses qualified in speciality to baby should be 1 nurse: 1 baby. This nurse should have no other managerial responsibilities during the time of clinical care but may be involved in the support of a less experienced nurse working alongside her in caring for the same baby.	1
High dependency care	The ratio of neonatal nurses qualified in speciality responsible for the care of babies requiring high dependency care should be 1 nurse: 2 babies. More stable and less dependent babies may be cared for by registered nurses not qualified in speciality, but who are under the direct supervision and responsibility of a neonatal nurse qualified in speciality.	0.5
Special care	The ratio of nurses looking after special care babies should be at least 1 nurse: 4 babies. Registered nurses and non-registered clinical staff may care for these babies under the direct supervision and responsibility of a neonatal nurse qualified in speciality. Staffing in special care must be sufficient to ensure that discharge is properly planned and organized, including adequate support for parents.	0.25

Table from British Association of Perinatal Medicine. (2022). *Service standards for hospitals providing neonatal care.*

1.5 Conclusion

In summary, preterm infants require a significant level of care due to the increased risk of developing short and long-term complications during their hospitalization. Resource allocation in the NICU can have important effects on the outcomes of patients. Specifically, the NPRs that infants receive during their hospitalization may influence their risk of mortality and/or morbidity. This relationship may be mediated by the care practices and interventions infants receive during their hospitalization which can influence their trajectory. There is, however, a lack of evidence in the literature to guide administrative decisions on the association between patient-level NPRs and outcomes.

Chapter 2 – Objective, Hypothesis and Research Questions

2.1 Objective

The objective of this study was to assess the association of NPR received on the shift of admission, in the first 24 hours, and the first 72 hours of admission with mortality and/or major morbidity among very preterm infants born <33 weeks GA.

2.2 Hypothesis

The current literature suggests a possible association between NPRs and patient outcomes. The hypotheses were formulated after the review of the literature.

H1: Infants that receive higher NPRs are at a lower risk of mortality and/or major morbidity in the first 72 hours of NICU admission.

2.3 Research Question

1. To determine if NPRs are associated with mortality and/ or morbidity among infants born <33 weeks.

Chapter 3 – Methodology

3.1 Research Strategy

3.1.1 Research Specification

The study aimed to assess the association between NPRs and neonatal outcomes. A correlational study design was utilized. Thus, we conducted a multicentre cohort study to evaluate the association between the independent variable (NPR) in the first 72 hours of NICU admission and its relationship with mortality and/or major morbidity among very preterm infants. We performed a retrospective analysis (secondary analysis) of prospectively collected data.

3.1.2 Validity of the Design

Internal Validity

Internal validity pertains to the method in which a study was designed, conducted and analyzed to reflect the true relationship between the variables being investigated without the influence of confounding factors or biases.[104] Important considerations related to internal validity in observational studies include confounding, selection bias and observation bias. In observational studies, the quality of our findings is significantly influenced by our ability to accurately identify, measure, and address potential confounding factors. Confounding occurs when a third variable influences both the exposure (independent variable) and the outcome (dependent variable) inducing a spurious statistical association.[105] As such, in this study we controlled for confounding by adjusting for patient characteristics and clinical risk in our analysis, using validated tools. To address selection bias, we try to ensure that the selection of the study participants was representative of the target population.[106] More specifically, infants were considered for our sample based on their admission to a Level 3 NICU in Canada over a period of time to ensure that all infants had a possibility of being included in the study population. Within each unit that participated in the study, all eligible patients were included. We also limited our study population to inborn infants, to avoid the possibility of transfer bias, as studies have shown that outborn infants are at higher risk of mortality and morbidity compared to inborn infants.[107] Moreover, Bradford Hill's criteria of temporality emphasizes that the exposure must precede the outcome,[108] however, in cases of transfer, there is a risk that infant outcomes may be influenced by other variables. Observation bias or ascertainment bias can also compromise the internal validity of a study when researchers or data collectors are not objective in their observations leading to a systematic error in data.[109] To minimize the risk of observation bias we used data collected from the CNN database that uses standardized and internationally recognized definitions when observing patient outcomes and characteristics.

In a correlational study, internal validity is based on the conformity between the theoretical model guiding the research and the statistical methods used to analyze the data.[105] In this study, the theoretical model was derived from previous literature examining risk adjustment methodology for neonatal outcomes.[72] The model was developed using expertise provided by neonatologists Dr. Marc Beltempo and Dr. Prakesh Shah, alongside biostatisticians Dr. Robert Platt and Eugene Woojin Yoon.

External Validity

External validity depends on whether the results of a study can be generalized to other contexts.[104] As such, to ensure our study findings can be generalized to populations other than the study population, we included patients and units that are diverse and representative of the target population. Sites were selected based on willingness to participate in the study. While participating units may have higher or lower nursing ratios and therefore a greater interest in the study, it's important to note that the 14 sites included encompass a diverse representation from different provinces across Canada. External validity in this study can be assessed from two perspectives: the extent to which the findings are generalizable to non-participating units in Canada and to units outside of Canada. As NICUs in Canada are regionalized and part of a public health care system, their organizational structure is relatively comparable.[96] Conversely, non-Canadian units may have notable differences in terms of healthcare systems, encompassing diverse frameworks that could impact resource allocation. As a result, our study findings may not be applicable to non-Canadian units.

3.2 Study Population

3.2.1 Target and Study Population

The target population for this study is very preterm neonates admitted to a Level 3 NICU. The study population consisted of all infants born at <33 weeks GA admitted alive to a Level 3 NICU in Canada. The inclusion and exclusion criteria for patients were as follows:

Inclusion Criteria

- Born <33 weeks GA
- Admitted to a Level 3 NICU in Canada between January 2020 and December 2021
- Inborn infant

Exclusion Criteria

- Outborn infant
- Moribund on admission (death in delivery room)
- Infants with major congenital anomaly

Note: Inborn patients include those that are delivered in a hospital with a Level 3 NICU, whereas outborn patients are those that are delivered in a hospital without a Level 3 NICU and require transport to a Level 3 unit after delivery due to their clinical status.

3.2.2 Empirical Estimation of Sample Size

An initial sample size of 1500 infants was established to be able to detect a 7% difference in the risk of death or major morbidity (estimated based on previous data) with a power of 80% and a type 1 error of 5% using the Fisher Exact test (assuming a 35% outcome rate).

We also compared the size to the number of patients included in similar studies. Neonatal studies of NPRs included between 692 and 2,675 patients.[8] A study that observed health outcomes in infants born at 23 to 32 weeks admitted to a Canadian NICU between 2004 and 2017 found that around 30.8% of newborns had the composite outcome of major mortality or morbidity.[1]

Considering the incidence of mortality and/or major morbidity in NICUs, it was reasonable to assume that a sample size of approximately 2,000 patients would be appropriate for this study.

3.2.3 Sampling Strategy

We used convenience sampling, a type of non-probability sampling method. Patient recruitment was based on birth and admissions to a Canadian hospital with a Level 3 NICU between January 2020 and December 2021. We selected units based on willingness to participate in the project in Canada and included all eligible patients based on the inclusion and exclusion criteria. We chose to recruit for a two-year period to increase the number of patients that fit the eligibility criteria, as on average, each neonatal unit in Canada admits 1,000 patients per year.[110]

3.3 Variable Definitions and Data Collection

3.3.1 Definition of Variables

Independent Variables

1. Nurse-to-patient ratio:
    - This variable was determined for each infant by applying the ratio received on the shift of admission or computing a mean NPR for the first 24 hours and the first 72 hours of admission (or until death, if occurred prior) for each infant.
    - NPRs that infants received could include 2 nurses per patient (NPR=2), 1 nurse per patient (NPR=1), 1 nurse per 2 patients (NPR=0.5), 1 nurse per 3 patients (NPR=0.3), and 1 nurse per 4 patients (NPR=0.25)

Dependent Variables

1. Composite outcome of mortality and/or major morbidity:
    - We used composite outcomes of mortality and/or major morbidity because they are common markers of quality of care in neonatal outcomes research, and are often used in

research examining quality of care in neonatology and they also have standardized definitions in the CNN database in which our data was acquired.[33,32]

- Mortality was defined as death during NICU hospitalization. Major morbidity was defined as the occurrence of one or more of the following complications: bronchopulmonary dysplasia (need for supplemental oxygen at 36 weeks postmenstrual age or at time of discharge if prior),[111] severe neurological injury (grade ≥3 intraventricular hemorrhage according to Papile et al.[62] and/or periventricular leukomalacia based on ultrasound findings), severe retinopathy of prematurity (stage ≥3 in at least one eye based on international classification or need for treatment with laser or ophthalmologic injection),[112] necrotizing enterocolitis (stage ≥2 according to Bell's criteria),[113] and nosocomial infection (positive blood or cerebrospinal fluid culture in a symptomatic neonate after 3 days in the NICU).
- Furthermore, a composite outcome was used to account for the competing events of mortality and major morbidity in preterm infants.[114] Neonatal death usually occurs in the first seven days of birth and morbidities typically arising later are connected to early interventions. Examining mortality alone might introduce selection bias, as critically ill infants who die prematurely could potentially have experienced major morbidity had they survived.[34]

Patient Characteristics

The following patient characteristics were measured: GA, BW, Small for Gestational Age (birth weight below 10th percentile [SGA]),[24] sex, use of antenatal steroids, SNAP-II score,[72] and 5-minute Apgar < 5.

3.3.2 Data Source, Collection and Quality

Data on patient characteristics, exposure (NPR received) and patient outcomes were extracted from the CNN database. The CNN is a consortium of all 32 tertiary NICUs in Canada that collect data on baseline characteristics, processes of care, and outcomes from all infants admitted at the sites.[17] Specifically for NPRs, data was obtained from patient charts or unit nursing assignment logs. A standardized definition for NPR at the patient-level was used to ensure accuracy and validity of our findings. At each site, patient information is entered electronically by trained abstractors into a data-entry program with built-in error checking that has shown high reliability and internal consistency.[115] The data was subsequently sent electronically to the CNN Coordinating Centre located at the Maternal-Infant Care Research Centre (MiCare) in Toronto, Ontario for analysis.

Lengths of scheduled nursing shifts were either 8 hours or 12 hours. Since the exact time of shift changes varied between units, participating sites were asked to report the NPR assigned to infants based on the start of shift corresponding to the following time windows [morning (6:00-9:00), afternoon (15:00-17:00), evening (19:00-21:00), and night (23:00-1:00)] of the study period. Since the duration of observation blocks varied between 4 hours and 8 hours, NPRs received were calculated for 4-hour observation blocks to ensure a harmonized analysis (e.g., an 8-hour block was split into two 4-hour blocks with the same NPR as the 8-hour block).

3.4 Data Analysis

The organizational characteristics of the unit and the infant characteristics included in the study were described using descriptive statistics. The mean and standard deviation were calculated for continuous variables with normal distributions, and the median with IQR for continuous variables with non-normal distributions. Categorical variables were described using the counts and proportions of patients in each category.

Logistic regression assumes that there exists a linear relationship between the independent variable and the logit of the dependent variable.[116] Thus, linearity between NPR (independent variable) as a continuous exposure variable and the logit of mortality and/or major morbidity (dependent variable) was verified visually using scatter plots and the Box-Tidwell test. The characteristics of infants with a health outcome of mortality and/or major morbidity were compared with those of infants without such an outcome. The organizational variables to which these two groups of patients were exposed were also compared.

Collinearity between the covariates was assessed using the variance inflation factor (VIF >5 was considered indicative of significant collinearity).[117] Due to strong collinearity between the 5-minute Apgar score and the SNAP-II, the 5-minute Apgar score was not included in model 2 or model 3 (described below). Both SNAP-II and 5-minute Apgar are associated with the degree of severity of the infant's clinical condition and are correlated.[118] The Quasilikelihood Information Criterion, which is used for model selection in the context of Generalized Estimating Equations (GEE) models, was employed to determine the most suitable model for the analysis of the correlated data.[119]

Multivariable logistic regression models were used to model the exposure and the outcome. Odds Ratios (OR) and 95% Confidence Intervals (CI) were then calculated. We applied three separate models to assess the association between the exposure and outcome. We adjusted for variables that occurred before the exposure (NPR) for each observation period. Model 1, which qualified as the birth model, was adjusted for variables that occurred before admissions, which includes, GA (continuous), SGA, sex, and Apgar <5. Adjustment variables for Model 2, the admissions model, were selected based on variables that occurred during admission which include GA (continuous), SGA, sex, and SNAP-II (continuous). Lastly, Model 3, or the first 24 hours model, was adjusted for variables that occurred in the first 24 hours, this includes for GA (continuous), SGA, sex, SNAP-II (continuous), and mode of ventilation on admission (no ventilation, non-invasive ventilation or invasive ventilation). A GEE approach was used to account for clustering within each site for each model.[120] This allowed us to account for the correlation of outcomes between patients within the same site.

Analyses were stratified by GA subgroup to account for the differences in recommended NPR which are based on GA (<29 and 29-32 weeks). Data management and statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3.5 Ethical Considerations

Approval for this project was obtained from the institutional Research Ethics Board of McGill University and each participating site and the CNN Executive Committee. The data was sent electronically from the participating sites to the Canadian Neonatal Network Coordinating

Centre located at the Maternal-Infant Care Research Centre (MiCare) in Toronto, Ontario. Patient information at every participating site is accessible exclusively to the respective site investigator and data abstractor. To maintain anonymity, before transferring data to the Coordinating Centre, patient identifiers were removed. The specific sites involved are not disclosed by name in this paper; instead, each site remains anonymous using randomly assigned numbers. At the Coordinating Centre, the central database is securely stored on a server, with an off-site backup managed and protected by the Mount Sinai Hospital Information Technology Department. The data collected was used solely for the present project and will be stored for 50 years on the CNN secure server.

Chapter 4 – Results: Article

Association of Nurse-to-Patient Ratios in the First 72 Hours of Admission and Outcomes of Very Preterm Infants: A Multicentre Cohort Study

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4.1 Abstract

Background: Very preterm infants born at <33 weeks Gestational Age (GA) are at high risk of short- and long-term complications. Neonatal Intensive Care Unit (NICU) organizational factors such as Nurse-to-Patient Ratios (NPRs) may contribute to patient outcomes. This study aimed to assess the association of NPRs received in the first 72 hours of admission with mortality and/or major morbidity among very preterm infants born <33 weeks GA.

Methods: This was a multicentre cohort study of inborn infants <33 weeks in 14 Level 3 NICUs in Canada between January 2020 and December 2021. Data on infant characteristics, NPRs and outcomes were obtained from the Canadian Neonatal Network database. NPR was recorded for the shift of admission, and a mean NPR was calculated for the first 24 hours, and first 72 hours of admission. Analysis was stratified by GA group to account for the differences in recommended NPR which are GA based (<29 and 29-32 weeks). Primary outcome was mortality and/or major morbidity. Three multivariable logistic regression models were fitted to estimate odds ratios adjusted for patient covariates with Generalized Estimating Equations to account for clustering within each site.

Results: The rate of mortality/major morbidity was 66% (633/952) among infants <29 weeks, and 19% (280/1501) among infants 29-32 weeks. The median NPR (Interquartile Range [IQR]) on shift of admission, first 24 hours, and first 72 hours were 1.00 [IQR 1.00-1.00], 1.00 [IQR 0.50-1.00], and 0.83 [IQR 0.53-1.00] for infants <29 weeks, and were 0.50 [IQR 0.50-0.50], 0.50 [IQR 0.50-0.75], and 0.50 IQR [0.50-0.58] for infants 29-32 weeks. In <29 week infants, there was insufficient precision and no evidence of an effect between higher NPRs received on the shift of admission (adjusted Odds Ratio (aOR); 0.63, 95% Confidence Interval (CI) 0.34-1.18), in the first 24 hours (aOR; 0.74, 95% CI 0.25-2.22), and in the first 72 hours (aOR; 0.82, 95% CI 0.24-2.76) of admission with mortality and/or major morbidity. Among infants born 29-32 weeks, higher NPR in the first 24 (aOR; 2.18, 95% CI 1.06-4.45) and 72 hours (aOR; 6.07, 95% CI 3.08-11.96) of admission were associated with higher odds of mortality and/or major morbidity.

Conclusion: Among infants born 29-32 weeks, higher NPRs in the first 24 and 72 hours of admission were associated with worse outcomes, which likely highlights confounding by

indication as sicker infants are more likely to receive higher NPRs. In the <29 week infants, we were unable to estimate a precise association between higher NPRs and mortality and/or major morbidity. Further intervention studies are required to evaluate if active interventions to improve NPRs and organizational care are associated with outcomes in the NICU.

4.2 Introduction

Very preterm infants born at <33 weeks gestational age (GA) are at high risk of short- and long-term complications.[1,2,3] Over 35% of them will either die or develop major neonatal morbidity during initial hospitalization.[4] Regionalization of neonatal care has significantly improved outcomes of very preterm infants by admitting these infants to specialized neonatal intensive care units (NICUs).[5,6,7] Although specialized NICUs have developed expertise in care, maintaining adequate human resources, particularly nurse staffing, is an ongoing challenge in most NICUs and may affect the quality of care.[8,9]

Importantly, care practices and interventions received in the first few days after birth (such as the successful use of non-invasive ventilation, time spent within target saturation, and minimal handling bundles) can have important effects on the risk of mortality or morbidity in very preterm infants. [4,10] Nurse-to-patient ratios (NPRs) may influence the ability to provide such interventions and subsequently affect infant outcomes. Previous studies have suggested an association between higher NPRs with lower risk for infection, missed nursing care, intraventricular hemorrhage and bronchopulmonary dysplasia in preterm infants. [9,11- 16]

Many studies have observed NPRs at the unit-level by evaluating the ratio of nurses per bed or the ratio of actual nurses available divided by the recommended number of nurses;[12] however, few studies have evaluated NPRs received at a patient-level and their association with outcomes in the NICU and results have been mixed.[13,17] The impact of patient-level NPRs have not been investigated in Canadian NICUs. Consequently, there is a need to evaluate whether and how NPRs received by very preterm infants are associated with outcomes. In this study we aimed to assess the association of NPR on the shift of admission, in the first 24 hours, and in the first 72 hours of admission with mortality and/or major morbidity among very preterm infants born <33 weeks GA.

4.3 Methods

4.3.1 Study design

This was a multicentre cohort study using a convenience sample of infants admitted to 14 Level 3 NICUs in the Canadian Neonatal Network (CNN) between January 2020 and December 2021. We included inborn infants (born in a hospital with a Level 3 NICU) with a GA of <33 weeks. We excluded outborn infants, infants that were moribund on admission or had a major congenital anomaly. Approval for this project was obtained from the institutional Research Ethics Board of McGill University and each participating site and the CNN Executive Committee.

4.3.2 Data Collection

Data on infant characteristics, NPRs received by infants and outcomes were obtained from the CNN database. Specifically for NPRs, data was obtained from patient charts or unit nursing assignment logs. At each participating site, trained abstractors collect data for each infant during their NICU stay according to a standard protocol, with information from patient charts entered electronically into a data entry program with a built-in error checking that has shown high reliability and internal consistency.[18] Patient characteristics included GA, birth weight, small for gestational age (SGA, defined as birth weight below 10th percentile),[19] sex, use of antenatal steroids, Score for Neonatal Acute Physiology-version 2 (SNAP-II),[20] mode of ventilation on admissions, and 5-minute Apgar < 5.

4.3.3 Exposure

Data on NPRs were obtained from nursing assignment logs in each site. Lengths of scheduled nursing shifts varied from 8 hours or 12 hours. Since the exact time of shift changes varied between institutions, sites were asked to report the NPR assigned to infants based on the start of shift corresponding to the following time windows [morning (6:00-9:00), afternoon (15:00-17:00), evening (19:00-21:00), and night (23:00-1:00)] of the study period. Since the duration of observation blocks varied between 4 hours and 8 hours, NPRs received were calculated for 4-

hour observation blocks to ensure a harmonized analysis (e.g., an 8-hour block was split into two 4-hour blocks with the same NPR as the 8-hour block). NPRs that infants received could include 2 nurses per patient (NPR=2), 1 nurse per patient (NPR=1), 1 nurse per 2 patients (NPR=0.5), 1 nurse per 3 patients (NPR=0.3), and 1 nurse per 4 patients (NPR=0.25). Missing data for NPRs (~4% of observation points) was imputed using the last observation carried forward for that infant.

For this study, we applied the NPR the infant received on the shift of admission, or we computed a mean NPR for the first 24 hours and the first 72 hours of admission or until death, if occurred prior. Previous studies have suggested that these time periods are critical in terms of care practices and interventions, and may contribute to mortality and/or major morbidity among very preterm infants.[4,10]

4.3.4 Outcomes

The primary composite outcome was mortality and/or major morbidity during hospitalization. A composite outcome was chosen because mortality, which usually occurs within the initial two weeks of life, and morbidities, typically arising later but connected to early interventions, represent competing events in very preterm infants.[21] Major morbidities included bronchopulmonary dysplasia (BPD; need for supplemental oxygen or respiratory support at 36 weeks postmenstrual age or at time of discharge if prior),[22] severe neurological injury (SNI; grade ≥3 intraventricular hemorrhage [IVH] according to Papile et al[23] and/or periventricular leukomalacia based on ultrasound findings), severe retinopathy of prematurity (ROP; stage ≥3 in at least one eye based on international classification[24] or need for treatment with laser or ophthalmologic injection), necrotizing enterocolitis (NEC; stage ≥2 according to Bell's criteria)[25] and nosocomial infection (NI; positive blood or cerebrospinal fluid culture in a symptomatic neonate after at least 3 days in the NICU). These major morbidities were included as they are used as markers of quality of care by the majority of neonatal outcome research and have standardized definitions.[5,26]

4.3.5 Statistical analysis

Descriptive statistics were used to summarize the data. The primary analysis used the NPR for the shift of admission or the mean NPR for the first 24 and 72 hours of admission as a continuous variable. Linearity between NPR as a continuous exposure variable and the logit of mortality and/or major morbidity was verified visually using scatter plots and using the Box-Tidwell test. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using multivariable logistic regression models to examine the association between NPR and outcomes. ORs represent the odds of the outcome for every increase in one nurse per patient. Three separate models were applied to assess the association between the exposure and outcome. Model 1, which qualified as the birth model, was adjusted for variables that occurred before admissions, which includes, GA (continuous), SGA, sex, and Apgar <5. Adjustment variables for model 2, the admissions model, were selected based on variables that occurred during admission which include GA (continuous), SGA, sex, and SNAP-II (continuous). Apgar <5 was excluded in the model due to its collinearity with SNAP-II. Lastly, model 3 or the first 24 hours model, was adjusted for variables that occurred in the first 24 hours, which includes GA (continuous), SGA, sex, SNAP-II (continuous) and mode of ventilation on admission (no ventilation, non-invasive ventilation or invasive ventilation). For each model, a Generalized Estimating Equations approach was used to account for clustering within each site.[27] Analyses were stratified by GA subgroup to account for the differences in recommended NPR which are based on GA (<29 and 29-32 weeks).

Several sensitivity analyses were conducted to assess the robustness of the results. Firstly, we used the exposures as a categorical variable for the shift of admission and the first 24 hours by categorizing infants into two groups: received 1:1 NPR for all blocks included in the specified exposure period vs. received <1:1 NPR for at least one block over the specified observation period. For the first 72 hours observation period, we assessed the association of the number of blocks (4-hour observation periods) with less than 1:1 NPR ratios with outcomes. Data management and statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

4.4 Results

Among 2617 eligible infants, 164 were excluded for pre-specified criteria (**Supplementary Figure 1**). The median number of infants per site was 162 [IQR 84-268]. Among the 2453 infants included in the analysis, the median GA was 29 [IQR 27-31] weeks and the rate of mortality/morbidity was 66% (633/952) among infants <29 weeks, and 19% (280/150) among infants 29-32 weeks **(Table 1)**. The median NPR on shift of admission, first 24 hours, and first 72 hours were 1.00 [IQR 1.00-1.00], 1.00 [IQR 0.50-1.00], and 0.83 [IQR 0.53-1.00] for infants <29 weeks, and were 0.50 [IQR 0.50-0.50], 0.50 [IQR 0.50-0.75], and 0.50 [IQR 0.50-0.58] for infants 29-32 weeks (Table 1). Overall, infants <29 weeks received higher NPRs than infants 29-32 weeks.

Among infants born <29 weeks, there was insufficient precision and no evidence of an effect between higher NPRs received on the shift of admission (adjusted Odds Ratio (aOR); 0.63, 95% CI 0.34-1.18), in the first 24 hours (aOR; 0.74, 95% CI 0.25-2.22), and in the first 72 hours (aOR; 0.82, 95% CI 0.24-2.76) of admission with mortality and/or major morbidity **(Table 2)**. In 29-32 week infants, NPRs in the first 24 hours (aOR; 2.18, 95% CI 1.06-4.45) and in the first 72 hours (aOR; 6.07, 95% CI 3.08-11.96) were associated with higher odds of mortality and/or major morbidity **(Table 2)**.

In the unadjusted analysis among infants born <29 weeks GA, higher NPRs on shift of admission, in first 24 and 72 hours of admissions were associated with higher odds of mortality **(Supplementary Table 1)**. Once adjusted for patient covariates, the point estimates were not statistically significant. In the sample of infants born at 29-32 weeks GA, higher NPRs on admission, in the first 24 and 72 hours of admissions were associated with higher odds of mortality **(Supplementary Table 1).**

Sensitivity analysis using exposures on the shift of admission and the first 24 hours as categorical variables (received only 1:1 vs. <1:1) yielded similar effect directions and results: there was insufficient precision and no evidence of an effect in the <29 week subgroup; however among infants born 29-32 weeks, 1:1 NPR in the first 24 hours was associated with higher odds of mortality and/or major morbidity (**Supplementary Table 2**). In addition, the number of shifts for which infants received <1:1 ratios in the first 72 hours also showed similar results to when using the mean NPR for the first 72 hours among infants born <29 weeks **(Supplementary Table 3)**.

4.5 Discussion

The results of this multicentre cohort study suggest that the association of higher NPRs in the first 24 and 72 hours with worse outcomes among infants 29-32 weeks likely highlights confounding by indication as sicker infants are more likely to receive higher NPRs. Among infants born <29 weeks, we were unable to estimate a precise association between higher NPRs received on the shift of admission, in the first 24 hours, and in the first 72 hours with mortality and/or major morbidity.

The increased risk of mortality and/or major morbidity in the first 72 hours of admission with higher NPRs among infants born 29-32 weeks GA is likely due to confounding by indication as previously described. This positive association observed in the 29–32 week GA subgroup, suggests that the observed relationship may not solely reflect the impact of nurse staffing, but rather the severity of illness influencing both nursing assignments and patient outcomes. The data showed that 29-32 weeks GA infants had more variability in NPR received for the first 24 hours, with 15% of infants receiving 1:1 nursing, suggesting that more acute infants had higher ratios. The rate of mortality and/or major morbidity in infants 29-32 weeks GA (19%) is also much lower than for infants <29 weeks GA (66%), suggesting that these are different populations and that separating them into subgroups for analysis may be more appropriate when looking at the association of NPR received with outcomes.

In the <29 week subgroup, although point estimates in the adjusted analysis suggested an association between higher NPRs on admission, in the first 24 hours and 72 hours of admission with lower odds of mortality and/or major morbidity, the 95% CI crossed 1 and may be attributable to sample size combined with confounding by indication. Studies observing the relationship between NPRs and neonatal outcomes have shown mixed results. For instance, Beltempo et al. found that infants born <29 weeks that had high nursing provision ratios had a lower risk of developing the composite outcome of mortality or major morbidity.[28] Overall, our findings, within the context of this multicentre study, suggest that the significance of NPR as an independent predictor of infant outcomes may not be as pronounced as suggested by smaller observational studies. This highlights the complexity of neonatal care and underscores the need for further research to better understand the multifaceted factors influencing neonatal outcomes.

The data showed that infants who were in a more critical condition were allocated higher NPRs within the initial 24 and 72 hours. Thus, the confounding by indication observed in this study may suggest that managers are modifying nursing ratios based on nursing needs of patients. Importantly, this study underscores that the GA of an infant should not be the only criteria in determining the NPR an infant receives. Critical factors to consider include need for respiratory support, nutritional support, and intravenous status, as GA is often correlated with these indicators. Thus, there should be more consideration for clinical status of the patient. As previously mentioned, most nursing guidelines recommend that infants born <29 weeks should receive 1:1 NPR in the first seven days after admission, however, this may not be realistic considering the availability of resources in the NICU. Our results show that 53% of infants <29 weeks received 1:1 nursing ratio for the first 24 hours which highlights that managers may be modifying nursing ratios in the context of finite human resources, which seems to be appropriate within the context of the 14 participating NICUs. In addition, mortality and/or major morbidity, however, is a complex outcome and may not be the most appropriate outcome when evaluating the impact of NPRs received in the NICU. Using a composite outcome may not adequately reflect the true significance of an exposure's impact on patient outcomes, as these outcomes may not have equal clinical importance. Alternatively, other studies have shown an association of NPRs with intermediate outcomes such as missed patient care, time spent with target saturation and nursing burnout.[16,29,30,31]

To our knowledge, this is the largest multicentre cohort study conducted to date to assess the association of patient-level NPRs in the first 72 hours of admissions with mortality and/or major morbidity in very preterm infants. This study used validated data and outcomes with detailed shift-by-shift data from multiple sites. We also collected and used individual patient-level nursing data for multiple shifts and observed the NPR received beyond the 24-hour observation period. Additionally, we applied multiple techniques to model the exposure and found consistent findings across methods.

Our study has limitations. The main one that was seen in this study was the confounding by indication despite adjusting for patient covariates.[32] We were unable to account for changes in patient clinical status across the days as we did not have additional measurements for patient acuity beyond 12 hours after birth. We also did not have data on nursing experience,[33] overtime,[34] burnout,[35] or unit occupancy[36] which could all influence the quality of care an infant receives and subsequently affect infant outcomes. We also observed low variability in NPR received in the first 24 hours of admission since infants born <29 weeks typically receive 1:1 NPR. The exposure, or NPR received by infants was not observed for the entire hospitalization period, so some of these outcomes are distant in relation to the timing of exposure. Lastly, the study took place during the COVID-19 pandemic, which may influence the generalizability of our findings outside the COVID-19 context.

4.6 Conclusion

The results in this multicentre cohort study showed that sicker infants received higher NPRs in the first 24 hours and 72 hours, suggesting that managers are modifying NPR assignments based on nursing needs during those timeframes. Similarly, the association of higher NPRs in the first 24 and 72 hours with worse outcomes among infants 29-32 weeks also highlights that sicker infants are more likely to receive higher NPRs. Among infants born <29 weeks, we were unable to estimate a precise association between higher NPRs with mortality and/or major morbidity. Further intervention studies are required to evaluate if active interventions improve NPRs and if organizational care is associated with outcomes in the NICU.

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Tables

Table 5. Table 1: Patient characteristics, nurse-to-patient ratios, and outcomes of infants by gestational age subgroup

Variables	**<29 weeks GA (n = 952)**	**29-32 weeks GA (n = 1501)**
Patient characteristics		
Antenatal steroids	913 (96)	1437 (96)
Gestational age, weeks	26 [25-27.50]	31 [30-32]
Birth weight, grams	850 [690-1050]	1530 [1314, 1770]
Male sex	517 (54)	803 (54)
Apgar at 5 min < 5	152 (16)	64 (4)
Small for gestational age	124 (13)	187 (12)
SNAP-II score > 20	246 (26)	76 (5)
Shift of admission		
Proportion of infants with 1:1 on every shift	647 (68)	450 (30)
Median NPR received	1.00 [1.00-1.00]	0.50 [0.50-0.50]
Mean NPR received	0.87 (0.33)	0.65 (0.26)
Median 4-hour blocks per infant received <1:1	0 [0-0]	1 [1-1]
First 24 hours		
Proportion of infants with 1:1 on every shift	505 (53)	225 (15)
Median NPR received	1.00 [0.50-1.00]	0.50 [0.50-0.75]
Mean NPR received	0.84 (0.27)	0.61 (0.20)
Median 4-hour blocks per infant received <1:1	0 [0-6]	6 [3-6]
First 72 hours		
Proportion of infants with 1:1 on every shift	343 (36)	90 (6)
Median NPR received	0.83 [0.53-1.00]	0.50 [0.50-0.58]
Mean NPR received	0.79 (0.24)	0.58 (0.17)
Median 4-hour blocks per infant received <1:1	7 [0-17]	18 [15-18]
Primary outcome		
Mortality/major morbidity	633 (66)	280 (19)
Secondary outcomes		
Mortality	129 (14)	19 (1)
Severe neurological injury	116 (12)	36 (3)
Bronchopulmonary dysplasia	491 (60)	224 (15)
Severe retinopathy of prematurity	91 (14)	9 (1)
Necrotizing enterocolitis	92 (10)	17 (1)

Nosocomial infection	200 (21)	43 (3)
Mortality/severe neurological injury	206 (22)	52 (3)

Abbreviations: GA, gestational age, NPR, nurse-to-patient ratio

Categorical data presented as n (%) and continuous data presented as mean (SD) or median [interquartile range].

A nurse-to-patient ratio of 0.5 to 1 corresponds to 1 nurse for 2 infants and represents the average ratio received over the observation period (shift of admission, first 24 hours or 72 hours).

Table 6. Table 2. Multivariable logistic regression analysis assessing the association of nurse-to-patient ratio*(on shift of admission, mean of the first 24 hours and mean of the first 72 hours of admission) with mortality and/or major morbidity stratified by gestational age subgroup

GA subgroup		**<29 weeks GA (n = 952)**	**29-32 weeks GA (n = 1501)**
Mortality/Major Morbidity		**Odd ratio (95% CI)**	
Shift of admission	**Crude**	1.24 (0.64, 2.41)	1.99 (0.96, 4.12)
	Adjusted Model 1	0.63 (0.34, 1.18)	1.43 (0.65, 3.12)
First 24 hours	**Crude**	1.96 (0.62, 6.22)	**4.57 (2.45, 8.56)**
	Adjusted Model 1	0.79 (0.27, 2.36)	**3.06 (1.65, 5.68)**
	Adjusted Model 2	0.74 (0.25, 2.22)	**2.18 (1.06, 4.45)**
First 72 hours	**Crude**	3.09 (0.85, 11.15)	**17.75 (9.73, 32.37)**
	Adjusted Model 1	0.99 (0.27, 3.60)	**11.72 (5.67, 24.24)**
	Adjusted Model 2	0.88 (0.25, 3.04)	**8.54 (4.42, 16.50)**
	Adjusted Model 3	0.82 (0.24, 2.76)	**6.07 (3.08, 11.96)**

Abbreviations: GA, gestational age; CI, confidence interval

Odds ratios were modelled using the NPR for the shift of admission, or the mean NPR for the first 24 hours and 72 hours of admission.

All models used a generalized estimating equations approach to account for the clustering within each site.

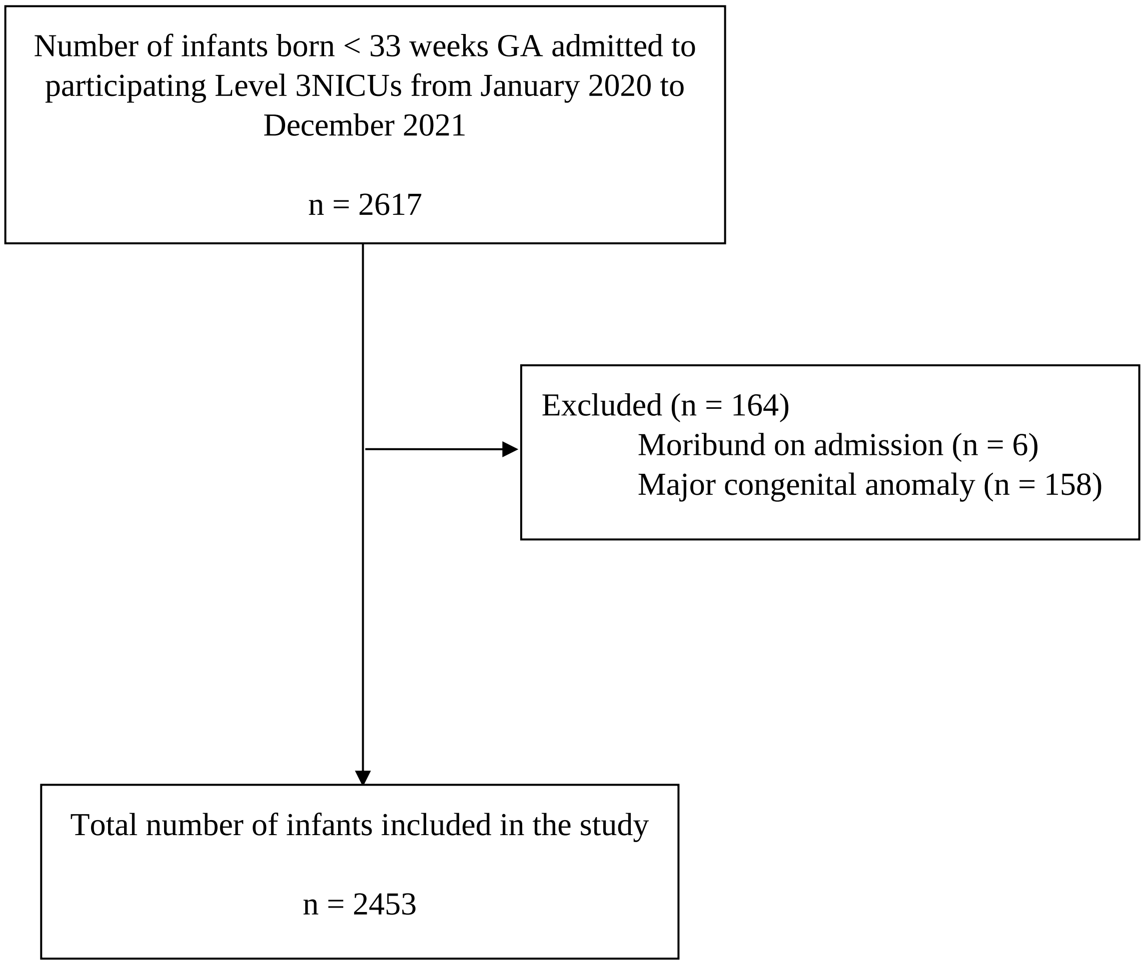
Model 1: adjusted for gestational age (continuous), small for gestational age, sex, and APGAR <5.

Model 2: adjusted for gestational age (continuous), small for gestational age, sex, and SNAP-II (continuous).

Model 3: adjusted for gestational age (continuous), small for gestational age, sex, SNAP-II (continuous), and mode of ventilation on admission.

Supplementary Figure

Figure 3. Supplementary Figure 1. **Study population flowchart**



Supplementary Tables

Table 7. Supplementary Table 1. Multivariable logistic regression analysis assessing the association of nurse-to-patient ratio*(on shift of admission, mean of the first 24 hours and mean of the first 72 hours of admission) with mortality stratified by gestational age subgroup

GA subgroup		**<29 weeks GA (n = 952)**	**29-32 weeks GA (n = 1501)**
Mortality		**Odd ratio (95% CI)**	
Shift of admission	**Crude**	**2.63 (1.79, 3.85)**	**12.05 (4.53, 32.09)**
	Adjusted Model 1	0.89 (0.49, 1.58)	**8.00 (2.66, 24.09)**
First 24 hours	**Crude**	**4.78 (1.99, 11.46)**	**48.18 (19.25, 120.59)**
	Adjusted Model 1	1.12 (0.49, 2.55)	**35.49 (14.24, 88.46)**
	Adjusted Model 2	0.81 (0.38, 1.74)	**18.19 (7.29, 45.40)**
First 72 hours	**Crude**	**7.76 (3.05, 19.70)**	**20.25 (5.10, 80.42)**
	Adjusted Model 1	1.39 (0.52, 3.74)	**11.91 (3.43, 41.38)**
	Adjusted Model 2	1.31 (0.46, 3.76)	**7.08 (1.46, 34.37)**
	Adjusted Model 3	1.26 (0.43, 3.71)	4.09 (0.76, 21.99)

Abbreviations: GA, gestational age; CI, confidence interval

Odds ratios were modelled using the NPR for the shift of admission, or the mean NPR for the first 24 hours and 72 hours of admission.

All models used a generalized estimating equations approach to account for the clustering within each site.

Model 1: adjusted for gestational age (continuous), small for gestational age, sex, and APGAR <5.

Model 2: adjusted for gestational age (continuous), small for gestational age, sex, and SNAP-II (continuous).

Model 3: adjusted for gestational age (continuous), small for gestational age, sex, SNAP-II (continuous), and mode of ventilation on admission.

Table 8. Supplementary Table 2. Multivariable logistic regression analysis assessing the association of nurse-to-patient ratios* (on shift of admission and the first 24 hours admission) as a categorical variable with mortality and/or morbidity stratified by gestational age subgroup

Outcomes	**Crude odds ratio**		**Adjusted odds ratio**	
	Shift of admission	**First 24 hours**	**Shift of admission**	**First 24 hours**
<29 weeks GA (n = 952)				
Mortality/major morbidity	1.17 (0.68, 2.00)	1.52 (0.89, 2.58)	0.74 (0.45, 1.21)	0.94 (0.57, 1.56)
29-32 weeks GA (n = 1501)				
Mortality/major morbidity	1.42 (0.84, 2.39)	2.38 (1.77, 3.19)	0.97 (0.58, 1.62)	**1.50 (1.09, 2.07)**

Abbreviations: GA, gestational age

Odds ratios were modelled by categorizing NPR: received 1:1 NPR for all blocks included in the specified exposure period vs. received <1:1 NPR for at least one block over the specified observation period.

Models adjusted for SNAP-II score >20, gestational age, small for gestational age, sex, and mode of ventilation on admission with generalized estimating equations to account for the clustering within each site.

Table 9. Supplementary Table 3. Multivariable logistic regression analysis assessing the association of the number of blocks with <1:1 nursing in first 72 hours (18 x 4-hour observation block) with outcomes stratified by gestational age subgroup

Outcomes	Crude odd ratio	Adjusted odd ratio
<29 weeks GA (n = 952)		
Mortality/morbidity	0.97 (0.93, 1.01)	1.01 (0.97, 1.05)
Mortality	**0.93 (0.88, 0.98)**	1.00 (0.96, 1.04)
Severe neurological injury	**0.94 (0.91, 0.97)**	0.977 (0.953, 1.002)
Bronchopulmonary dysplasia	**0.965 (0.933, 0.998)**	1.00 (0.97, 1.04)
Severe retinopathy of prematurity	**0.951 (0.904, 0.999)**	1.031 (0.995, 1.068)
Necrotizing enterocolitis	0.96 (0.91, 1.01)	1.00 (0.96, 1.04)
Nosocomial infection	0.98 (0.93, 1.03)	1.03 (0.99, 1.08)

Abbreviations: GA, gestational age

Odds ratios were modelled using NPR as infants received 1:1 NPR for all blocks during the observation period vs. infants that's did not receive 1:1 NPR for all blocks during the observation period.

Models adjusted for SNAP-II score >20, gestational age, small for gestational age, sex, and mode of ventilation on admission with generalized estimating equations to account for the clustering within each site.

Note: The 29-32 week subgroup was not observed for this analysis as majority of infants were assigned <1:1 nursing in the first 72 hours of admission

Chapter 5 – Supplementary Results

Some results were not presented in the article in Chapter 4.

Table 10. Nurse-to-patient ratios stratified by infant outcomes

Variables	Infants with mortality/ major morbidity	Infants without mortality/ major morbidity
Number of infants	913	1540
Median NPR received		
Shift of admissions	1 (0.5, 1)	0.5 (0.5, 1)
First 24 hours	0.75 (0.5, 1)	0.5 (0.5, 0.75)
First 72 hours	0.75 (0.5, 1)	0.5 (0.5, 0.67)
Proportion of infants with 1:1 NPR on every shift		
Shift of admissions	542 (59)	562 (36)
First 24 hours	422 (46)	292 (19)
First 72 hours	288 (33)	124 (9)

Abbreviations: NPR, nurse-to-patient ratio

Categorical data presented as n (%) and continuous data presented as median [interquartile range].

Table 11. Multivariable logistic regression analysis assessing the association of nurse-to-patient ratios* (on shift of admission, mean of the first 24 hours and mean of the first 72 hours of admission) with mortality and morbidities stratified by gestational age subgroup

Outcomes	Crude odds ratio			Adjusted odds ratio		
	Shift of admission	First 24 hours	First 72 hours	Shift of admission	First 24 hours	First 72 hours
<29 weeks GA (n = 952)						
Mortality	**2.63 (1.79, 3.85)**	**4.78 (1.99, 11.46)**	**7.76 (3.05, 19.70)**	0.79 (0.47, 1.34)	0.90 (0.43, 1.89)	1.31 (0.45, 3.78)
Severe neurological injury	**2.44 (1.75, 3.39)**	**4.20 (1.77, 9.97)**	**7.19 (3.25, 15.93)**	1.13 (0.74, 1.72)	1.44 (0.65, 3.19)	**2.78 (1.18, 6.55)**
Bronchopulmonary dysplasia	1.11 (0.57, 2.13)	2.39 (0.92, 6.17)	3.28 (1.16, 9.34)	**0.45 (0.24, 0.85)**	0.86 (0.32, 2.28)	0.98 (0.33, 2.89)
Severe retinopathy of prematurity	**2.37 (1.33, 4.20)**	**2.93 (1.19, 7.23)**	**3.56 (1.34, 9.47)**	0.54 (0.24, 1.21)	0.33 (0.10, 1.12)	**0.31 (0.10, 0.94)**
Necrotizing enterocolitis	1.27 (0.74, 2.16)	1.58 (0.60, 4.15)	**3.13 (1.05, 9.31)**	**0.56 (0.36, 0.88)**	0.51 (0.24, 1.11)	0.87 (0.30, 2.52)
Nosocomial infection	1.66 (0.88, 3.16)	1.70 (0.54, 5.38)	2.21 (0.49, 9.83)	0.73 (0.38, 1.38)	0.50 (0.16, 1.54)	0.43 (0.08, 2.24)
29-32 weeks GA (n = 1501)						
Mortality	**12.05 (4.53, 32.09)**	**48.18 (19.25, 120.59)**	**20.25 (5.10, 80.42)**	**3.52 (1.27, 9.73)**	**9.32 (3.21, 27.05)**	2.82 (0.43, 18.44)
Severe neurological injury	**4.11 (2.47, 6.85)**	**9.54 (3.81, 23.94)**	**26.02 (8.08, 83.77)**	1.87 (0.97, 3.63)	**3.08 (1.48, 6.40)**	**8.95 (2.93, 27.35)**
Bronchopulmonary dysplasia	1.50 (0.54, 4.14)	**4.06 (1.95, 8.45)**	**11.14 (4.88, 25.44)**	0.78 (0.25, 2.46)	1.50 (0.61, 3.65)	**4.21 (1.76, 10.08)**
Severe retinopathy of prematurity	2.11 (0.07, 64.28)	4.00 (0.05, 318.99)	**11.51 (1.40, 94.63)**	N/A	N/A	N/A
Necrotizing enterocolitis	**3.85 (1.34, 11.03)**	**5.90 (1.71, 20.40)**	**6.90 (2.29, 20.84)**	2.77 (0.89, 8.63)	4.95 (0.90, 27.19)	5.26 (0.96, 28.97)

Nosocomial infection	2.24 (0.95, 5.25)	**3.42 (1.43, 8.14)**	**5.40 (1.85, 15.77)**	1.16 (0.48, 2.78)	1.23 (0.46, 3.28)	1.58 (0.60, 4.17)

Abbreviations: GA, gestational age

Odds ratios were modelled using the NPR for the shift of admission, or the mean NPR for the first 24 hours and 72 hours of admission.

Models adjusted for SNAP-II score >20, gestational age, small for gestational age, sex, and mode of ventilation on admission with generalized estimating equations to account for the clustering within each site.

N/A: Not applicable as model could not be fitted due to low event rates

Table 12. Multivariable logistic regression analysis assessing the association of nurse-to-patient ratio*(on shift of admission, average of the first 24 hours and average of the first 72 hours of admission) with with process indicators stratified by gestational age subgroup

Outcomes	**Crude odds ratio**			**Adjusted odds ratio**		
	Shift of admission	**First 24 hours**	**First 72 hours**	**Shift of admission**	**First 24 hours**	**First 72 hours**
<29 weeks GA (n = 952)						
Normothermia on admissions	0.69 (0.42, 1.15)	N/A	N/A	0.88 (0.47, 1.66)	N/A	N/A
NPO >2 days after birth	2.58 (1.31, 5.07)	5.30 (2.97, 9.46)	N/A	1.58 (0.63, 3.95)	**3.20 (1.31, 7.84)**	N/A
Success of non-invasive ventilation in first 7 days	0.21 (0.09, 0.47)	0.10 (0.03, 0.43)	0.05 (0.01, 0.31)	0.60 (0.27, 1.36)	0.44 (0.16, 1.17)	0.27 (0.07, 1.01)
Success of non-invasive ventilation in first 7 days among those not intubated in delivery room	0.26 (0.09, 0.78)	0.14 (0.03, 0.66)	0.08 (0.01, 0.44)	0.58 (0.19, 1.78)	0.42 (0.10, 1.81)	0.26 (0.05, 1.36)
29-32 weeks GA (n = 1501)						
Normothermia on admissions	1.01 (0.41, 2.48)	N/A	N/A	1.10 (0.44, 2.80)	N/A	N/A
NPO >2 days after birth	2.14 (0.70, 6.55)	8.82 (1.74, 44.79)	N/A	1.00 (0.30, 3.39)	3.26 (0.59, 18.12)	N/A
Success of non-invasive ventilation in first 7 days	0.23 (0.11, 0.49)	0.07 (0.03, 0.16)	0.02 (0.01, 0.07)	0.39 (0.18, 0.84)	**0.13 (0.05, 0.33)**	0.04 (0.01, 0.13)
Success of non-invasive ventilation in first 7 days among those not intubated in delivery room	0.39 (0.23, 0.66)	0.16 (0.06, 0.39)	0.05 (0.01, 0.26)	0.53 (0.32, 0.87)	0.26 (0.11, 0.63)	**0.08 (0.02, 0.42)**

Abbreviations: GA, gestational age; NPO, nil-per-os

Odds ratios were modelled using the NPR for the shift of admission, or the mean NPR for the first 24 hours and 72 hours of admission.

Models adjusted for SNAP-II score >20, gestational age, small for gestational age, sex, and mode of ventilation on admission with generalized estimating equations to account for the clustering within each site.

N/A: Not applicable as model could not be fitted due to low event rates

Chapter 6 – Discussion

6.1 Summary of Study and Results

The aim of this multicentre cohort study was to evaluate the association of NPRs with mortality and/or major morbidity among very preterm infants in the NICU. The finding showed an association between higher NPRs in the first 24 and 72 hours with worse outcomes among infants 29-32 weeks, which highlights that sicker infants are more likely to receive higher NPRs. Furthermore, among infants born <29 weeks, there was insufficient precision and no evidence of an effect between higher NPRs received on the shift of admission, in the first 24 hours, and in the first 72 hours with mortality and/or major morbidity.

6.2 Confounding by Indication

Confounding by indication is a source of bias commonly seen in observational studies. It occurs when an apparent association between an exposure and an outcome is influenced or distorted by the underlying health condition or severity of illness for which the exposure is indicated. As a result, we are more likely to see an association between infants who are sicker, exposed to better interventions or resources, and experience worse outcomes. To illustrate, further analysis stratifying infants with mortality/major morbidity and those without showed that infants that died or developed major morbidity had a higher proportion of shifts in which they received 1:1 NPR for all blocks in the specified exposure period **(Table 10)**.

Watson et al. conducted a study with the aim of evaluating the effects of one-to-one NPR on the mortality rate in the NICU. The authors highlighted that NPR studies at the individual patient-level have not been able to adequately address unobserved confounding, which may occur due to higher-risk infants being more likely to receive more intensive nursing care.[11] They also underlined the concept of reverse causality, where the clinical status of infants is causing the one-to-one nursing provision. Consequently, if infant health is not accurately observed, study findings may underestimate the benefits or even show adverse effects of one-to-one nursing as a result of unobserved confounding. This limits the ability to observe the true effects of the NPR on infants' clinical outcomes.

In the literature, certain patient characteristics are known to be associated with higher or lower risks of neonatal complications.[121] In particular, the following were selected for statistical adjustment: sex, GA at birth, SGA, Apgar at 5 minutes, SNAP-II score, and mode of ventilation. In other words, we considered patient characteristics as potential confounders, and therefore adjusted for them, since they may be associated with both our exposure and our outcome. In neonatal research, the primary set of confounders, which include GA, sex, and SGA, are typically adjusted for, regardless of statistical or clinical significance.[114] The second set of covariates are adjusted depending on the data or literature. We adjusted for sex as being born female has been associated with better outcomes.[122] The literature shows that survival in preterm infants tends to increase with increasing GA, as such the risk of mortality and morbidities is inversely related to GA.[123] SGA refers to infants whose birth weight is below the 10th percentile for their GA, causing them to be at a higher risk for adverse outcomes.[24] Apgar score at less than 5 minutes (Apgar <5 min) is a numerical assessment that evaluates the physical condition of a newborn immediately after birth to predict neonatal survival.[124] SNAP-II is a validated neonatal severity of illness score used to control for patient acuity on presentation and the inherent predisposition to worse outcomes and as a result NPR they are assigned.[72] We adjusted for mode of ventilation on admission as the type of ventilation that an infant receives is generally an indicator of the recommended NPR. This type of ventilation can also have an impact on adverse outcomes. For instance, invasive ventilation has been associated with an increased risk of BPD.[39] Further, infants born 29-32 weeks that are on mechanical ventilation should receive 1:1 NPR, depending on their stability. Thus, by including mechanical ventilation in our analysis we are accounting for the fact that if an infant is on mechanical ventilation, they should be getting a higher NPR. Overall, by adjusting for confounding variables, we want to isolate the specific effect of NPR on patient outcomes, minimizing the impact of other factors that could distort the results.

Further, we used the SNAP-II score, which comprises of six scoring items: temperature, urine output, blood pressure, seizure, pH, PaO2/FiO2 ratio. Although the SNAP-II tool is useful for adjusting patient acuity in statistical analyses, it has some limitations. This includes temporal limitations; the score is calculated based on a single assessment during the first 12 hours of the infant's life. As a result, changes in the infant's clinical status are not reflected across hospitalization days. Since adverse outcomes are more likely to occur among sicker infants who are also more likely to receive higher NPR than infants who are less ill, this raises concerns for confounding by indication. Thus, the increased risk of mortality or major morbidity in this study may be linked to the indication for patient acuity rather than to the NPR itself.

Moreover, a recurrent challenge encountered in neonatal studies is the absence of a universal index measure of baseline level of illness severity.[114] Several different measures of baseline level of severity of illness have been used in neonatal research studies such as baseline probability of death, neurological developmental impairment or receiving mechanical ventilation for the first 7 days of life.[114] For instance, a study assessed whether early nutritional support provided to sicker infants differs from that provided to less sick infants during the initial weeks of life. The study used the receival of mechanical ventilation during the first seven days of life to reflect the severity of illness of the infant.[125] The authors acknowledge that using this measure for assessing severity of illness has limitations compared to utilizing a validated severity of illness score, such as the Clinical Risk Index for Babies. In the context of this study, there are several unmeasured confounders that we could not adjust for, such as respiratory severity score and hemodynamic instability which may have reduced the bias seen in our results.[126] However, despite statistical adjustment, confounding by indication may still be reflected in the results. This is highlighted in the observed variation in the adjusted OR when including more confounder variables into the model. In addition, there is concern for over adjustment which could also influence the study findings.

6.3 Morbidities

We conducted additional analysis to observe the association between the NPRs received by infants on the shift of admission, in the first 24 and 72 hours of admission with each individual morbidity (BPD, SNI, ROP, NEC, and NI) **(Table 11)**. The findings showed that among infants born <29 weeks, higher NPRs on the shift of admission were associated with lower odds of BPD and NEC, but higher odds of SNI in the first 72 hours of admission. This observed association between higher NPR in the first 72 hours with higher odds of SNI could be attributed to the fact that the highest risk period for acute brain injury is in the first 72 hours post-birth, thus it is more likely to be detected during this period.[127] Similarly, among the 29-32 week subgroup, higher NPRs were associated with higher odds of morbidities across the exposure periods. Overall, these results are indicative of confounding by indication.

The association of higher NPRs on shift of admission with better outcomes in infants <29 weeks can be contrasted with the observed opposite effect when using a longer observation period (higher NPRs in the first 72 hours associated with worse outcomes such as SNI); this finding may highlight the limits of observational studies for NPRs. Indeed, the NPR received on admission might be due to random variation of available resources as NICU managers do not yet know the disease severity/patient acuity and try to maintain a 1:1 NPR for admission. However, as time progresses the NPR received may become more biased by indication since managers prioritize higher ratios for sicker infants. From an observational perspective, this random variation may allow us to better evaluate the effect of 1:1 nursing on patient outcomes when observing only the shift of admission (since the managers do not know how sick the baby will be prior to admission). Further, as the infant's acuity remains elevated on each shift and NICU resources remain strained, the NPR received becomes more biased due to indication despite statistical adjustment: managers prioritize higher ratios for sicker infants which would explain the association of higher NPRs in the first 72 hours with higher odds of SNI. This is consistent with previous studies that have shown varied results between nurse staffing and NICU outcomes.[10,95]

Moreover, the data also highlights that NICU managers strive to provide 1:1 NPR to infants born <29 weeks, regardless of their clinical status. As a result, we may compromise staffing for other patients to some degree. This could be due to the expectation that infants born <29 weeks will be sicker, leading to the belief that higher staffing will benefit them. In some situations, even when infants may be doing well, they will receive high NPR and may even receive care from more experienced staff. On the other hand, infants born 29-23 weeks are expected to be less sick, and people may not inherently believe a high NPR is as beneficial for them. Consequently, higher NPRs are not routinely assigned to infants born 29-32 weeks. As a result, infants in this GA range likely need to exhibit more severe symptoms to be assigned a higher NPR, and this effect likely intensifies over the initial 72 hours as their health condition becomes more apparent.

6.4 Process Indicators

Supplementary analysis was conducted to examine the association between NPR with process indicators: maintenance of normothermia on admission (recorded admission temperature between 36.5°C and 37.5°C),[73] successful use of non-invasive ventilation in the first seven days (not intubated),[128] and early initiation of feeds (nil per os [NPO] less than two days after birth),[129] during the observation periods, stratified by GA subgroup **(Table 12)**.

When looking at process indicators, higher NPRs were generally associated with higher odds of being NPO >2 days and lower odds of successful management without invasive mechanical ventilation. These results also highlight the correlation between disease severity and high nursing ratios received, in which the association between the exposure and clinical outcomes may be confounded or influenced by the underlying health status of the infants.

6.5 Discussion on Research Hypothesis

Our study found a significant association between higher NPRs in the first 24 and 72 hours and the risk of mortality and/or morbidity among infants born 29-32 weeks. However, it is important to acknowledge that we cannot assume causality in observational studies, as we were not able to control or manipulate the exposure. There are many factors that may have influenced this relationship between the exposure and outcome.

Importantly, NPR is a quantitative measure that does not give insight into the quality of nursing care which may influence patient outcomes. It is important to acknowledge that the NPR alone does not provide a comprehensive understanding of the quality of nursing care given to patients, which is multifaceted. Neonatal outcomes are influenced not only by the quantity of nursing staff but also by nursing skill mix, use of evidence-based practices[130] and the ability to provide individualized care. Thus, to systematically assess and improve neonatal care, both quantitative and qualitative factors must be considered.

This association may be influenced by other factors such as nursing experience, as improved NPRs may not address the skill mix and experience of nurses.[90] Studies have shown a relationship between nurse skill mix and the quality of care delivered.[100] In addition, nursing overtime can lead to increased fatigue and burnout among nursing staff, which may influence the quality of care and can contribute to adverse outcomes in preterm infants.[91] Further, overtime may contribute to emotional and psychological factors which may in turn influence care practices given such as hand hygiene, central line maintenance and patient skin care.[7] Additionally, higher NPR may be associated with increased handling and as a result may have deleterious effects on the infant's health.[82]

It's also important to note that infant outcomes are unlikely to solely be attributed to the interventions delivered by a single professional group, rather it is a result of various organizational factors and the transdisciplinary team (physicians, nurses, pharmacists, respiratory therapists, nutritionists, etc.).[100] Needleman et al. also highlighted that nurse staffing level is an incomplete measure of the quality of nursing care. As such, factors such as effective communication between healthcare professionals and the work environment have also been found to influence outcomes of patients.[79]

Moreover, the observed difference between the two subgroups can be explained by how nursing care is allocated based on GA. Infants born <29 weeks are more likely to receive 1:1 nursing in the first 72 hours of admission, aligning with nursing guidelines. Conversely, infants in the 29–32 week subgroup may receive either 1:1 or 1:2 NPR. Generally, sicker infants are more likely to receive higher NPRs and are also at a greater risk of experiencing adverse outcomes. Consequently, the positive association observed between higher NPRs and higher odds of mortality and/or major morbidity may be influenced by confounding by indication. This occurrence, more evident in the 29–32-week GA subgroup, suggests that the observed association may not solely reflect the impact of nurse staffing but rather the severity of illness influencing both nursing assignments and patient outcomes.

6.6 Strengths and Limitations

6.6.1 Strengths

This is the largest multicentre cohort study conducted to date to assess the association of patient-level NPRs for multiple shifts with neonatal patient outcomes in Canada. Importantly, this study contributes to the limited body of evidence on this topic as most studies tend to observe NPRs at the unit-level. The data was collected prospectively and acquired from the CNN database, a validated database with an error-checking system, which reduces the risk of information bias.[115] Additionally, we used validated data and outcomes, which limits the risk of information bias. We also had detailed shift-by-shift data obtained for the first 72 hours of admission. This enabled in-depth analysis of the relationship between the exposure and its impact on neonatal outcomes. We included multiple Level 3 units across Canada to ensure our study population was representative of the entire population, increasing the generalizability of our results. Furthermore, we applied multiple techniques to model the exposure and found consistent findings across methods, confirming the robustness of the results. Lastly, since our study population included infants hospitalized in the NICU, no patient was lost to follow-up, minimizing the risk of selection bias.

6.6.2 Limitations

Our study has limitations. The main one that was observed in this study was confounding by indication despite adjusting for patient covariates in our statistical models. More specifically, we were unable to account for changes in patient clinical status across the days as we did not have additional measurements for patient acuity beyond 12 hours after birth. The SNAP-II score was used as a predictor of mortality and/or major morbidity, however, it only accounts for various physiological variables that are measured in the first 12 hours of birth. As a result, we are unable to correct for the patient's clinical status in the first 24 hours and 72 hours of birth. We also did not have data on nursing experience,[95] overtime,[5] burnout[92] or unit occupancy[9] which could all influence the quality of care an infant receives and subsequently affect infant outcomes. Importantly, NPR is a quantitative measure that does not give insight into the quality of nursing care which may influence patient outcomes.[10]

We also observed low variability in NPR received in the first 24 hours of admission since infants born <29 weeks typically receive 1:1 NPR. The data showed that 68% of infants born <29 received 1:1 on the shift of admission, and 53% received 1:1 in the first 24 hours of admission. Consequently, the uniformity in NPR received within this GA subgroup during this timeframe limits our ability to discern the potential impact of varying staffing levels on neonatal outcomes.

Statistical methods are limited in terms of effectively addressing confounding by indication. Moreover, the ability to evaluate both the exposure and outcome is constrained to the variations in these variables within our study sample, potentially limiting the power to establish an association. In the context of this study, although we observed some degree of variation NPR received it was limited. As such, our study sample may be underpowered to detect any existing association between the nursing ratios and infant outcomes.

The exposure, or NPR received by infants, was not observed for the entire hospitalization period, so some of these outcomes are distant in relation to the timing of exposure. This limits our ability to capture the complete effect of NPRs on neonatal outcomes as the exposure is continuously changing throughout the entire hospitalization period. Importantly, future studies should adopt a more comprehensive and continuous observational framework by observing the NPR infants receive during their entire hospitalization.

Lastly, the study took place during the COVID-19 pandemic, which may influence the generalizability of our findings outside the COVID-19 context. However, a study was conducted to investigate neonatal outcomes of very preterm infants admitted to Canadian NICUs during the COVID-19 pandemic compared to the pre-pandemic period, comparing care practices and interventions between the two periods. The findings did not show an impact of the pandemic on NICU-based outcome processes.[131]

6.7 Implications

6.7.1 Implications for Management

Infants born <29 weeks often present with varying needs and complications that require specialized care. As such, assigning one nurse per patient may not be feasible in certain situations. The clinical status of an infant (beyond gestational age based criteria) may play a crucial role in managing the balance between providing optimal care and acknowledging the limitations of resources. Current recommendations of 1:1 nursing for all <29 week infants do not consider the clinical status of the infant. In the case of infants born <26 weeks, 1:1 NPRs may be the most appropriate in certain circumstances, specifically neuro-support, as there is an increased risk of neurodevelopmental impairments in infants born at <26 weeks' gestation.[132]

Additionally, adopting a Family-Integrated Care (FICare) approach may serve as a strategy to help mitigate periods of high nursing workload. FICare in the NICU is an approach that involves parents in providing direct care to their infants.[133] Studies have shown an association between FICare and improved infant feeding, growth and parent well-being and self-efficacy.[133] These factors play a crucial role in contributing to long-term improvements in infant neurodevelopmental and behavioural outcomes. The shift towards FICare may allow nursing managers to assign higher NPRs to sicker infants that require more care and as a result, improve the quality of care delivered.

6.7.2 Implications for Research

In this study, we used mortality and/or the occurrence of major morbidities as the health outcome. These are complex outcomes that may not reflect the quality of care delivered by nurses. Thus, future studies should explore associations between nursing ratios and intermediate process indicators such as missed patient care, time spent with target saturation, central line maintenance, and hand hygiene.[4,134,135,12] These intermediate outcomes may provide a better understanding of the impact of nursing ratios on patient care. Moreover, a study assessing the association between nursing ratios and acute deterioration of infants is an avenue of research that may provide better insight into optimal NPRs for high-risk infants.

There are ethical considerations concerning intervention studies on nursing ratios and patient outcomes. Specifically, conducting studies that systematically allocate a lower nursing ratio to a group of infants while providing a higher nursing ratio to another group raises ethical concerns. While our study findings showed mixed results, the high correlation between lower patient acuity and lower nursing ratios limits the evaluation of the effect of NPR in that group. To address this limitation and further explore the relationship between NPR and patient outcomes, one potential avenue is conducting a study focused on evaluating the association of a higher NPR with the outcomes of lower acuity infants. For instance, infants born between 29-32 weeks with a low SNAP-II score could be considered. This approach aims to discern whether aiming for a higher NPR in this specific subgroup is associated with improved outcomes. Alternatively, studies can also assess the impact of adhering to "mandatory" NPRs within the unit over a pre-specified time period. This approach recognizes the potential impact of policy interventions on nursing ratios and patient outcomes, facilitating a comprehensive evaluation of the multifaceted factors involved in the neonatal care setting.

Conclusion

This study assessed the association between NPRs and mortality and/or major morbidity among very preterm infants born <33 weeks GA. Among infants born 29-32 weeks, higher NPRs in the first 24 and 72 hours of admission were associated with worse outcomes, which likely highlights confounding by indication as sicker infants are more likely to receive higher NPRs. In the <29 week infants, we were unable to estimate a precise association between higher NPRs and mortality and/or major morbidity. This is the largest multicentre cohort study conducted to date that examines the association between NPRs and neonatal outcomes. The findings contribute to the body of literature evaluating the association between organizational care factors and patient outcomes. Further qualitative and quantitative studies are needed to confirm these results and determine optimal resource allocation management.

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Appendix A: Ethics Board Approval

Centre universitaire de santé McGill | McGill University Health Centre

Annual renewal submission form - Harmonized

Protocol title: **Impact of resource allocation on outcomes of very preterm infants in the NICU**

Project number(s): **MP-37-2021-6783**

Nagano identifier: **Resource Allocation**

Principal investigator: **Dr Marc Beltempo**

Project's REB approbation date: **2020-07-07**

Form: **F9H-113016**

First submit date: **2023-05-03**

Last submit date: **2023-05-03**

Form status: **Form approved**

Administration - REB

1. **MUHC REB Panel & Co-chair(s):**
   Pediatrics (PED), reb.peds@muhc.mcgill.ca

2. **REB Decision:**
   Approved - REB delegated review

3. **Renewal Period Granted:**
   From 2023-07-07 Until 2024-07-06

4. **Date of the REB final decision & signature**
   2023-06-26

   Signature

   Ms. Elizabeth Craven
   Coordinatrice du CER du CUSM | MUHC REB Coordinator
   pour le pour le co-président du CER du CUSM | for the MUHC REB Co-Chair
   2023-06-26 15:38

5. **List of participating sites for which the REB decision applies:**

   - CHU Sainte-Justine
   - CHU de Québec-Université Laval
   - CIUSSS de l'Estrie-CHUS
   - McGill University Health Centre

6. **Participating sites not included in the decision of the reviewing REB:**

We hereby advise the institutions mentioned below who's ethics approval has not been renewed at the time of the project's anniversary, that they must cease all research activities in accordance with article 5.3.2 of REB-SOP 406-001, and take the necessary steps to ensure the safety of research participants in their institutions.

CIUSSS-COMTL

The annual renewal form specific to the institution mentioned above was not submitted when the present annual renewal form or group of forms were initially reviewed. To verify the status of this institution and its renewal date, please refer to form

F9H - 113018

7. **Local REB number**

IRB00010120

8. **Note:**

In order to be in compliance with Good Clinical Practices, the MUHC REB (when acting as the Reviewing REB), and the PM of the MUHC does not directly communicate with sponsors. The communication channels existing between the PIs and the sponsors will continue to ensure the transmission of documents.

General information

1. **Indicate the name of the Principal Investigator in our institution (MUHC)**

Beltempo, Marc

From which department is the principal investigator?

Pediatrics

Division

Neonatalogy

Required information for renewal

1. **Date when the research project is expected to end at your institution:**

Date unknown

Please indicate (approximately) in what year you expect the project to end.

2024

2. **Indicate the current status of the research project at your institution:**

Chart review or basic sciences only (without recruitment)

Indicate the status of the data collection

Collection finished (analysis is in progress)

3. **Briefly describe in a few lines, the current status of the project:**

Data collection is complete at all sites, and is currently being validated. Preliminary analysis is underway.

4. **Please indicate the type of "participants" implicated in your research project**

Data related to individuals (project using data only)

Did you obtain all the data / samples you needed for the realization of your project as described in the protocol?

Yes

5. **In terms of what you are responsible to report, over the past year, relative to the situation at the time of the last REB renewal (or initial approval):**

Have there been any unreported changes to the REB affecting the study documents?

No

Were there unanticipated problems, serious adverse reactions, major deviations or other events or information altering the ethical acceptability or balance between risks and benefits of the project that were not reported to the REB?

No

Were there any temporary interruptions to the project?

No

Have the results of the project been submitted for publication, presented or published?

No

Should the REB be notified of a conflict of interest situation (of any kind) affecting one or more members of the research team, that was not reported at the time of the last approval of the project?

No

Has there been an allegation related to a breach in ethical compliance (eg: complaint from a participant, non-compliance with rules relating to ethics or integrity) concerning one or more researchers?

No

Does the sponsor require the submission of minor deviations from the protocol or other report that does not identify any impact on participant safety?

No

Participating sites without Nagano

1. **Is one of the sites participating in this project not using the Nagano platform**

No (this question can be modified by the REB)

Signature

Answer of: Patel, Sharina

1. **I certify that the information provided on this form is correct.**

Sharina Patel
2023-05-03 20:52

Appendix B: Data Access Approval

Canadian Neonatal Network™/ Le Réseau Néonatal Canadien (CNN)

Nov 21, 2022

Application for Access to CNN Data – Approval

Applicant(s): Marc Beltempo, Sabah Pirwani and investigators

Project Title: The Association of Nurse-to-Patient Ratios with Outcomes of Very Preterm Infants

Dear Marc and investigators,

Thank you for submitting your application for access to CNN Data for the project named above.

Your request was forwarded to the Canadian Neonatal Network Executive committee (CNN EC) for review.

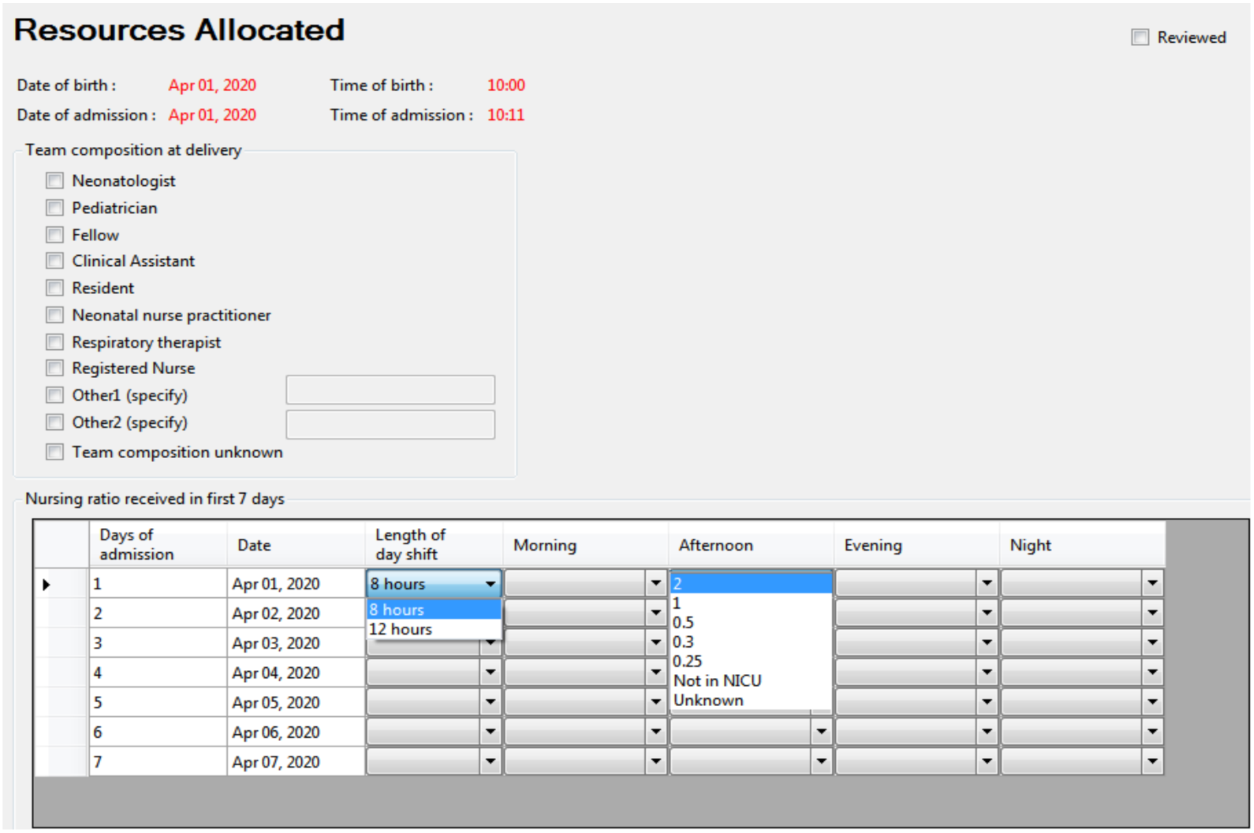
I am pleased to inform you that your application has been approved by the CNN Executive committee (CNN EC).

If you have any questions, please do not hesitate to contact me or Nevetha Balachandran, Nevetha.Balachandran@sinaihealthsystem.ca or 416-586-4800 ext 4935.

Sincerely,

Dr Prakesh Shah on behalf of the CNN Executive Committee

Appendix C: Data Collection Matrix for Nurse-to-Patient Ratio



Resources Allocated

☐ Reviewed

Date of birth : Apr 01, 2020   Time of birth : 10:00

Date of admission : Apr 01, 2020   Time of admission : 10:11

Team composition at delivery

- ☐ Neonatologist
- ☐ Pediatrician
- ☐ Fellow
- ☐ Clinical Assistant
- ☐ Resident
- ☐ Neonatal nurse practitioner
- ☐ Respiratory therapist
- ☐ Registered Nurse
- ☐ Other1 (specify)
- ☐ Other2 (specify)
- ☐ Team composition unknown

Nursing ratio received in first 7 days

Days of admission	Date	Length of day shift	Morning	Afternoon	Evening	Night
1	Apr 01, 2020	8 hours		2		
2	Apr 02, 2020					
3	Apr 03, 2020					
4	Apr 04, 2020					
5	Apr 05, 2020					
6	Apr 06, 2020					
7	Apr 07, 2020					

Length of day shift options: 8 hours; 12 hours

Afternoon options: 2; 1; 0.5; 0.3; 0.25; Not in NICU; Unknown

Appendix D: Recommended Nurse-to-Patient Ratio

Supplementary Table 1: Recommended nurse-to-patient ratios according to admission day status

Admission Day Status	WANNNT	BAPM	AAP
<26 – NIMV	1:1	1:1	1:1
<26 IMV	1:1	1:1	1:1
26-28 NIMV	1:1	1:1	1:1
26-28 IMV	1:1	1:1	1:1
29-32 RA	0.3:1	0.25:1	0.3:1
29-32 NIMV	0.5-0.7:1	1:1	0.5-1:1
29-32 IMV	0.5-0.7:1	1:1	0.5-1:1

Abbreviations: WANNNT, Winnipeg Assessment of Neonatal Nursing Needs; BAPM, British Association of Perinatal Medicine; AAP, American Academy of Pediatrics; NIVM; non-invasive mechanical ventilation, IMV; invasive mechanical ventilation; RA; relative adjusted

*The WANNNT recommends 1:1 for all <29 week infants in the first seven days of admission
* The UK recommends 1:1: for all <29 week infants in the first two days or first five days if they are on any respiratory support for all gestational ages