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Providing clarity around ethical discussion: Development of a neonatal intervention score (NIS)

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Short Title:
Development of a neonatal intervention score (NIS)

Abstract:
Aim: To develop a neonatal intervention score to describe the clinical trajectory of a neonate throughout their neonatal intensive care unit (NICU) admission.
Methods: The Neonatal Intervention Score (NIS) was developed by modifying the Neonatal Therapeutic Intervention Scoring System (NTISS) to reflect illness severity, dependency on life-sustaining interventions and overall life trajectory on a longitudinal basis, rather than illness burden. Validity for longitudinal use within the NICU was tested by calculating the score for 99 preterm babies born less than 28 weeks at predetermined time points throughout their admission to tertiary level care at two institutions.
Results: A total of 1333 NISs were analysed, ranging from 0 to 32.5 (mean 9.77, SD 5.4). Internal consistency (Cronbach alpha) reached 0.8. NIS moderately correlated to both SNAPPE-II and SNAP-II (Spearman's rho= 0.47, p=<0.001) within the first 24 hours.
Conclusion: The NIS is a useful and reliable descriptive tool of relative illness severity and degree of medical interventions throughout a baby's admission. Integrating a longitudinal description of medical dependency of a patient may assist both clinical and ethical decision-making and empirical research by

providing an objective account of a baby's clinical trajectory. Establishment of validity within individual institutions is required.

Keywords: Decision-making, ethics, preterm neonates

Key notes:

There are no tools for clinical or research purposes that describe a neonate's dependency on life-sustaining interventions throughout their Neonatal Intensive Care Unit admission.

The Neonatal Intervention Score (NIS) is a consistent measure of what clinicians 'do to' neonates throughout their admission as distinct from a prognostication tool based on data around the time of delivery. It may facilitate rigorous empirical ethics research and optimize communication between providers and parents.

INTRODUCTION

With advancing technology, critically unwell neonates that eventually die are surviving longer (1). This has raised concern that NICUs are overtreating patients and subjecting them to expensive and burdensome treatment unnecessarily (2, 3). Yet, even when neonates are predicted to do poorly, there can be significant medical uncertainty around how to weigh up the benefit-to-burden ratios of ongoing interventions. This leads to significant challenges in counselling families and in decision-making. Disagreements about how best to proceed, due to differing assessments of illness severity and likely outcomes, can result in significant moral distress where some healthcare providers feel constrained to provide ongoing treatment they believe is not in the patient's interests (4-6).

Traditionally, estimates of outcome are made on population-based outcomes and use perinatally derived risk factors including gestational age, birthweight, gender, provision of antenatal steroids and whether the baby was inborn within a tertiary level NICU (7). Though existing tools such as NICHD calculator (8) and PREM score (9) may be useful for initial counselling around the time of delivery, such scores do not account for any clinical changes in the baby throughout the admission. Increasingly, physicians are seeking less arbitrary and more individualised approaches that are adjusted for progression within the NICU. Andrews *et al*, for example, demonstrated the added prognostic ability of a normal cranial ultrasound and clinician intuitions in predicting survival when compared with the prenatal markers alone (7). Though clinician intuitions provide additional prognostication, they remain too subjective and inaccurate to form the basis for end-of-life decisions (10, 11). Other commonly used tools such as SNAP-II and SNAPPE-II take into consideration physiological parameters and are used to predict mortality, benchmark units and to evaluate cost-effectiveness or resource utilisation (12, 13). However, these too are only validated for use within the first 24 hours of life. Additionally, obtainment of an arterial gas for the SNAPPE-II is not always practical or clinically appropriate. Furthermore, both these scores become less predictive for individual mortality or severe disability with increasing length of stay in the NICU (14-16).

The National Therapeutic Intervention Scoring System (NTISS), developed by Gray *et al*, was created to reflect disease severity based on interventions rather than by pathophysiological measurements. Though the authors intended to validate its use for serial measurements, to our knowledge this was never performed beyond the first few of days of life (17). Furthermore, on review of the NTISS, some components

appeared to be weighted towards perceived burden for a patient rather than illness severity *per se*. For example, the use of an antiepileptic was given the low score of 1 in the NTISS. Although the administration of such a medication is of a low burden to the patient, in the preterm brain the presence of seizures suggests neurological injury and increases the likelihood of long term poor neurodevelopmental outcomes (18-20). A tool to describe the relative illness severity of a patient (rather than intervention burden) at a point in time and longitudinally throughout admission is therefore still lacking.

The aim of this study was to create a Neonatal Intervention Score (NIS) and assess its validity and reliability in describing the clinical trajectory and dependence on technology within population of preterm babies admitted to two intensive care units. The NIS was initially designed in the context of longitudinal research into moral distress and/or empiric bioethics; consistent application and standardisation of the NIS was intended to provide a more objective account of patient wellbeing and identify cases where, for example, care is potentially burdensome, or conversely where the distress experienced by caregivers is disproportionately high compared with the clinical trajectory of an individual infant. A broader application of the NIS however is anticipated and possible uses within clinical and research environments will be discussed.

PATIENTS AND METHODOLOGY:

The Neonatal Intervention Score (NIS) was developed by modifying the National Therapeutic Intervention Scoring System (NTISS). The NTISS was first reviewed for applicability of items given changes in standard neonatal practices since the development of the NTISS. Three of the authors (TP, PD, AJ) deliberated on what other variables may distinguish illness severity longitudinally. Scores were adjusted to reflect implied illness severity rather than burden – this most significantly affected the value of medications including post-natal steroids and anticonvulsants. Similar to the NTISS, items were subdivided into systems categories. (See Table 1 for comparison of the NTISS items and weighting compared to the NIS.) The score was piloted on 20 preterm neonates born < 28 weeks using retrospective case review. Face validity was then sought from a panel of practitioners including four neonatologists and one neonatal intensive care nurse to review the appropriateness of both inclusion and weighting of each item. At the time of data collection the item 'indwelling catheter' was dropped from the score due to inconsistent documentation and realisation that its presence often reflected level of sedation rather than illness

severity *per se*. The final score for each day was calculated as the total of the highest clinical score for each category (i.e. Respiratory + FiO_2 + Cardiovascular + Medications + Nutrition + Blood Products + Lines + Surgery). Values containing a letter represent mutually exclusive items within a category. Where this was applicable, only the most heavily weighted item within each category was included within the final score. Given the additive nature of the intervention score, there was no maximum score. Within the score, the NIS does not distinguish between types of surgery; the complexity of the surgery is captured by the increase of additional interventions. Example 1 illustrates a NIS calculation.

To evaluate the utility of the NIS, NISs were calculated prospectively in a cohort of 99 preterm babies born less than 28 weeks that had been admitted consecutively to a tertiary level perinatal intensive care unit in Melbourne, Australia between 2016 and 2017. For babies requiring transfer to the nearby quaternary centre for surgical intervention or High Frequency Jet Ventilation, data collection continued following transfer. Ethics approval was granted for data collection at both centres.

NISs were calculated for each infant on days 0, 1, 3, 5, 7, 9, 14, 21, 28 and every two weeks thereafter (or weekly if still ventilated) until discharge from tertiary level care. Each NIS was based on the maximal interventions that each baby received on that day (i.e. the highest NIS per individual baby). Neonatal demographic details were obtained on day 0. Outcome data including death or discharge location, length of stay and final diagnoses were collected.

Statistical analysis

Internal consistency of the NIS was evaluated using Cronbach's alpha. Whilst the NIS is intended as a descriptive rather than a predictive score, it is necessary to show that it is able to discriminate between sick and well neonates over time. Scores reflecting the first 24 hours of life were therefore examined in relation to established markers of illness severity (SNAP-II and SNAPPE-II) and mortality outcome. These markers were chosen to enable comparison with the NTISS. Illness severity scores were compared using Spearman rank correlation, Student's t-test and equality of medians.

Life Trajectories

NIS over time was plotted for the surviving cohort. The distribution of NISs for the entire cohort for each day of collection was displayed graphically (Figure 1). In order

to include all surviving patients on each day, patients discharged home, not requiring any further interventions, were given a score of 0. For patients discharged to a level two unit, NIS were imputed by graduating the score to a score of 0 at the predicted time of discharge. NISs were also plotted according to classifications of death as noted by Verhagen *et al* (21); redirection due to physiological instability required two of the following: persistent desaturation despite 100% oxygen on mechanical ventilation, hypotension despite volume infusion and inotropes, protracted bradycardia or anuria for >24hours.

Example 1:
A baby on high frequency oscillatory ventilation in a baseline of 70% oxygen, on antibiotics with a long line and receiving 25% of her nutrition via TPN and the other 75% via NGT would receive a score of:
HFOV: (5) + FiO_2 (3) + Antibiotics (1)+ TPN (3) + Central line (2) = 14

RESULTS:

A total of 99 consecutively admitted babies born <28 weeks were followed from birth to discharge from tertiary level care (1 neonate had been excluded from analysis due to early demise prior to consent being obtained). The demographic characteristics of included infants are shown in table 2. Length of stay ranged from 1 day to 198 days (mean 93.3 days, SD 41.5). 1333 NISs were calculated (100% of intended collection points) with a mean score of 9.8 (SD 5.4). Scores ranged from 0 to 32.5. There was good internal consistency with a Cronbach alpha of 0.80.

Relationship to neonatal data

Within the first 24 hours mean NIS did not significantly differ between genders (mean NIS males = 15.0 (SD 4.3), mean NIS females = 14.5 (SD 3.9), $p = 0.52$) or between inborn babies (born within the treating hospital) compared with outborn neonates (mean NIS inborn = 14.5 (SD 4.0), outborn = 15.6 (SD 4.5), $p = 0.26$). NIS correlated weakly with birthweight (Spearman's rho = 0.31) and corrected gestational age (Spearman's rho = 0.29), though as expected the more immature, born <25 weeks, were more likely to have a higher NIS within the first 24 hours ($p = 0.03$) than babies born at 25-<28 weeks.

Relationship to in-Hospital Mortality:

During the study period 13 babies died. These babies had a higher NIS within the first 24 hours (mean NIS = 20.1 (SD 5.6)) than survivors (mean NIS = 14 (SD 3.2), $p = <0.001$). Peak NIS throughout admission was also significantly higher in non-

survivors (mean peak NIS = 24.6 (SD 5.0)) compared with survivors (mean peak NIS = 16.4 (SD 4.7), p = <0.001). The mean NIS on the day of death was 17.2 (SD 8.4). SNAP-II and SNAPPE-II scores were available for 78/99 patients (79%): SNAPPE-II scores were not able to be calculated for 21 infants for whom an arterial gas was not available. NIS within the first 24 hours was moderately correlated to both SNAPPE-II and SNAP-II (Spearman's rho = 0.47, p = <0.001). Within this cohort, ten of the non-survivors died within the first month. The median NISs were significantly higher for the non-survivors compared to the survivors at each of the pre-determined time-points within the first month (figure 1 and table 3).

DESCRIBING THE TRAJECTORY OF PRETERM BABIES:

Given the internal consistency and the persisting validity of the NIS throughout time, we have used the NIS to plot the trajectory of a cohort of preterm babies. This enables comparison of one neonate's progress to other similar babies within a particular institution assuming clinical care practices are relatively consistent. Figure 2 demonstrates the distribution of NIS for the entire cohort.

For comparison, the life trajectories of all non-survivors are shown (by different colored lines) in figure 3 according to categorization of death (21). The variability in trajectory reflects the variation in reason for redirecting the goals of care and withdrawing life-sustaining interventions. Four babies died on the ventilator where families had declined recommendations to remove the endotracheal tube when ongoing intensive care was no longer considered in the patient's interests. A further two babies had their endotracheal tube removed in the setting of imminent death with parental consent. Seven babies were electively redirected in the setting of predicted poor outcomes. One of these babies was critically unwell following post-operative complications but was regaining physiological stability at the time of redirection.

Discussion:

End-of-life decision making within the NICU remains a highly complex and challenging task for clinicians and families. Tools to assist individualised and transparent decisions are desired, yet to date no such tool exists beyond the first few days of life (14). Being able to describe relative illness severity and dependency on life-sustaining interventions of a patient over the course of an intensive care admission is important in order to weigh up the ethical implications of clinical practice. This is the first study to longitudinally utilise such a score for descriptive rather than predictive purposes. That this tool correlates moderately well with current

illness severity scores and distinguishes between surviving and non-surviving babies within the first month supports its validity as a tool to describe illness severity and life trajectory. Furthermore, unlike the SNAPPE-II, the NIS does not rely on arterial blood gases which may be impractical or clinically inappropriate throughout a neonate's admission.

The NIS may be used to describe the life trajectory of preterm babies in many different kinds of empirical investigations, particularly but not limited to investigations exploring the appropriateness of interventions or continuing intensive care. A pictorial representation may assist in providing clarity about the degree of intervention required compared with other similar aged babies and shed light on time-points where the neonate's trajectory has not improved as expected or has regressed. The longitudinal utilisation of the score enables the clinical trajectories of different cohorts of patients to be described, potentially shedding light on previously underappreciated patterns or outliers. Once validated for different settings and categories of patients, this score could be used for longitudinal empirical research including analysing parental experiences and perspectives and changing patterns of utilisation for particular technologies.

It is important to highlight this tool should not be used to predict outcomes but to promote review and constructive discussion. Clinical context must be considered. For example, elective surgery including closure of stoma or laser therapy for retinopathy of prematurity will raise the score without implying increased likelihood of mortality. However, the increase in NIS remains of ethical and clinical significance if, for example, the burdens of the interventions are not believed to be in the patient's interests.

With further research, it is possible that the pictorial description of one baby's trajectory when compared to an institution's norm could be developed into a counselling tool for families, either to provide reassurance that a baby is taking an expected clinical course, or to highlight where the baby's course is deviating from the norm. This may be particularly useful in babies with chronic conditions where the baby has failed to track along the expected trajectory but a lack of clear deterioration makes it difficult for families to comprehend that the prognosis is becoming more concerning with time. Conversely, it may also serve to reassure an anxious family – where the baby is following the anticipated trajectory – that their babies is doing well. Further use of the NIS within empirical bioethics studies will determine its utility.

Limitations:

We acknowledge that practices vary from institution to institution. This score therefore requires validation in other institutions. Furthermore, this score was limited to testing in a population of preterm babies born <28 weeks with further research in this cohort intended. Validity therefore needs to be tested for babies outside of this gestational age range with a broader range of diagnoses.

Conclusions:

The Neonatal Intervention Score (NIS) is a reliable and useful descriptive tool for highlighting the relative illness severity and dependency on life-sustaining interventions or clinical trajectory of one baby compared to other similar babies. Once validated within individual institutions, the NIS may facilitate more robust and objective empirical research, highlight patients benefiting from review of their care plan and optimize communication between clinicians and parents.

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Potential Conflicts of Interest:

The authors have no conflicts of interest relevant to this article to disclose.

Abbreviations

NICU: Neonatal intensive care unit

NIS: Neonatal interventions score

NTISS: Neonatal therapeutic intervention scoring system

SNAP-II: Score for Neonatal Acute Physiology (version II)

SNAPPE-II: Score for neonatal acute physiology perinatal extension (version II)

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Table 1. Comparison of NIS with NTISS

INTERVENTION	NIS	NTISS
RESPIRATORY		
No support/RA	0	0
LFNP	1a	1a
Surfactant	N/A	1
Tracheostomy care	N/A	1b
Tracheostomy placement	4	1b
CPAP/HFNP	2a	2a
NIPPV	3a	N/A
CMV	4a	3a
CMV with relaxation	N/A	4a
HFOV	5a	4a
HFJV	6a	N/A
FiO2		
RA	0	
<40%	1b	N/A
40-60%	2b	N/A
61-90%	3b	N/A
>90%	4b	N/A
iNO	7	N/A
CARDIOVASCULAR		
Nil intervention	0	
Volume expansion (</= 15ml/kg)	N/A	1c
Volume expansion (>15ml/kg)	N/A	3c
1 inotrope	1c	2d
2 inotropes	2c	3d
>/=3 inotropes	3c	N/A
Hydrocortisone	4c	N/A
Pacemaker on standby*	N/A	3e
Pacemaker used*	N/A	4e
Cardiopulmonary Resuscitation (CPR)	5	4
MEDICATION		
Antibiotic/antifungal/antiviral administration (</=2 agents)	1	1f
Ibuprofen/Indomethacin	2	1
Diuretic administration (enteral)	N/A	1g
$NaHCO_3$ (NTISS-treatment of Metabolic Acidosis)	3	3
Phenobarbitone/anticonvulsant	4	1
Post Natal Steroids (DART)	5	1
Post Natal Steroids (Cummings/prolonged course)	6	N/A
Aminophylline administration	N/A	1
Other unscheduled medication	1	1
Antibiotic administration (>2 agents)	N/A	1f
Potassium binding resin administration	N/A	3
Insulin	4	2
Potassium infusion	N/A	3
Phototherapy	N/A	1
Monitoring		
Frequent vital signs	N/A	1
Phlebotomy (5-10 draws)	N/A	1h
Thermoregulated environment	N/A	1
Noninvasive O_2 monitoring	N/A	1
CVP monitoring	N/A	1
Quantitative input and output	N/A	1
Extensive phlebotomy (>10 blood draws)	N/A	2h
Cardiorespiratory monitoring	N/A	1
Nutrition		
Full suck	0	0
NGT <25%	0.5d	1
NGT <50%	1.5d	N/A
NGT <75%	2d	N/A
NGT <100%	2.5d	N/A
TPN <50%	3d	N/A
TPN >50%	3.5d	N/A
NBM/trophic	4d	N/A
Lines (score for items multiplied by number		
Intravenous line (IV)	0.5	1
Indwelling catheter (IDC)	N/A	1
Peripherally inserted arterial line (PIA)	1.5	1
Central venous access	2	2
Chest drain (single)	2.5	2j
Multiple chest drains	N/A	3j
Pericardial tube in place*	4	4l
Blood Products (item score multiplied by number of transfusions required)		
PRBC (<-15ml/kg in NTISS)	1	2i
PRBC > 15ml/kg	N/A	3i
Platelets	2	3
FFP/Cryoprecipitate	3	N/A
20% Albumin	4	N/A
IVIG*	3	1
White blood cell transfusion*	N/A	3
Double volume exchange transfusion*	N/A	3
Surgery	4	4l
Transport of a patient	N/A	2
Pericardialcentesis*	N/A	4l
ECMO*	4	4

*Denotes items not applicable to out cohort of patients

Table 2. Neonatal demographics

	Survivors	Non-survivors	p value
n	86	13	
Gestation mean (SD)	26.0 (1.2)	25.0 (1.5)	0.005
Birthweight (g) mean (SD)	832 (176)	766 (252)	0.235
SNAP-II	21.6 (11.9)	33.4 (18.4)	0.021
SNAPPE-II	41.0 (20.2)	63.2 (23.6)	0.003
Gender			
Male	44	4	0.170
Female	42	9	0.170
Complete Antenatal Steroids >/=2 doses	60	7	0.257
1 min APGAR mean (SD)	4.1 (2.3)	2.3 (1.8)	0.009
5 min APGAR mean (SD)	6.6 (2.1)	4.2 (2.6)	<0.001
10 min APGAR mean (SD)	8.0 (1.2)	5.5 (3.1)	<0.001
Inborn	65	12	0.175

Table 3. Comparison of NIS for Survivors compared with Non-Survivors

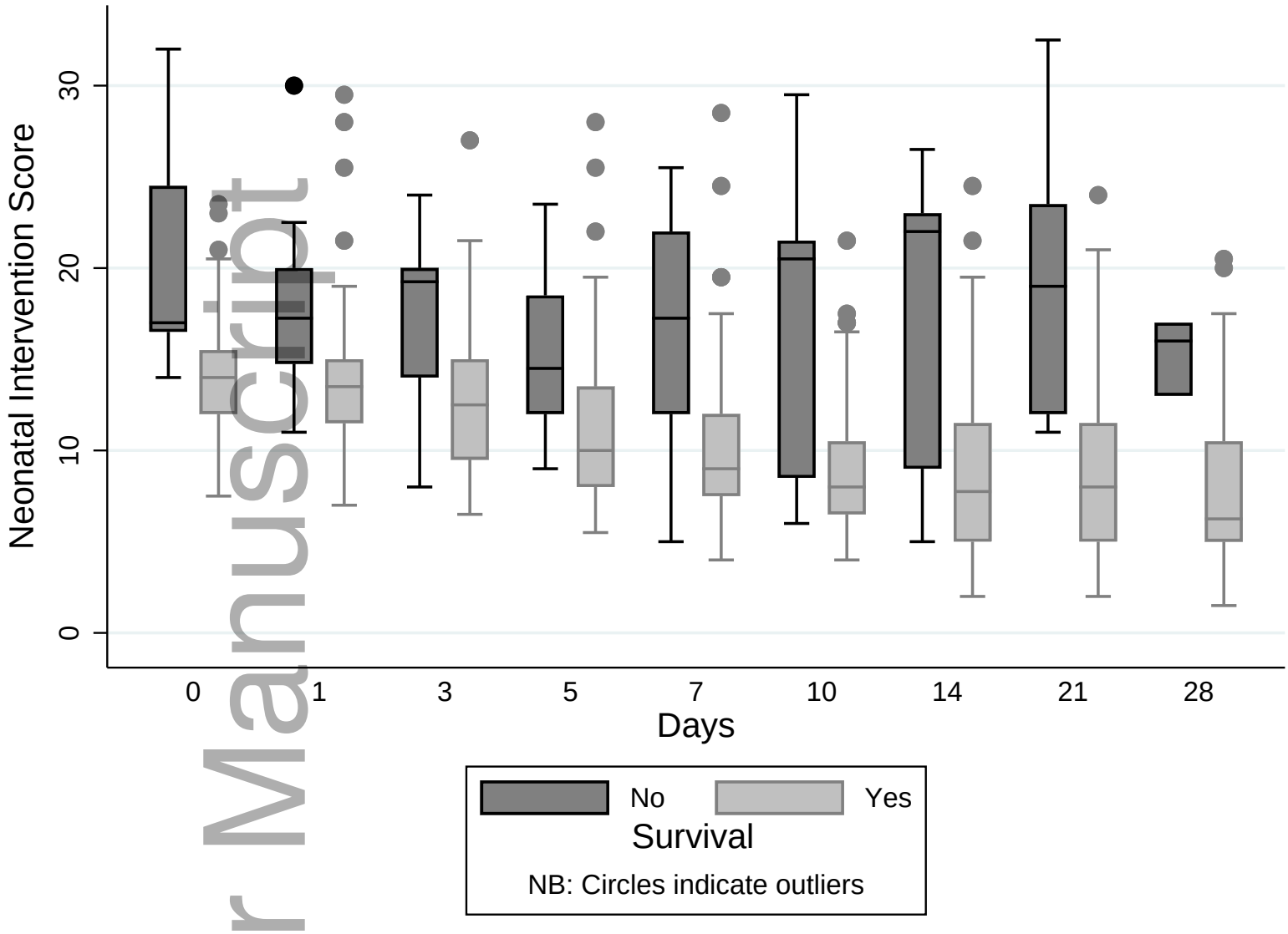
Day	Equality-of-medians *p*
0	0.002
1	0.01
3	0.009
5	0.01
7	0.03
10	0.04
14	0.12
21	0.01
28	0.08

Figures:

Figure 1. Comparison of NIS for survivors versus non-survivors across the first month of life.

Figure 2. Distribution of NIS for preterm babies born <28 weeks.

Figure 3. Life Trajectories of non-surviving babies according to categorization of death compared with the NIS distribution of surviving babies.



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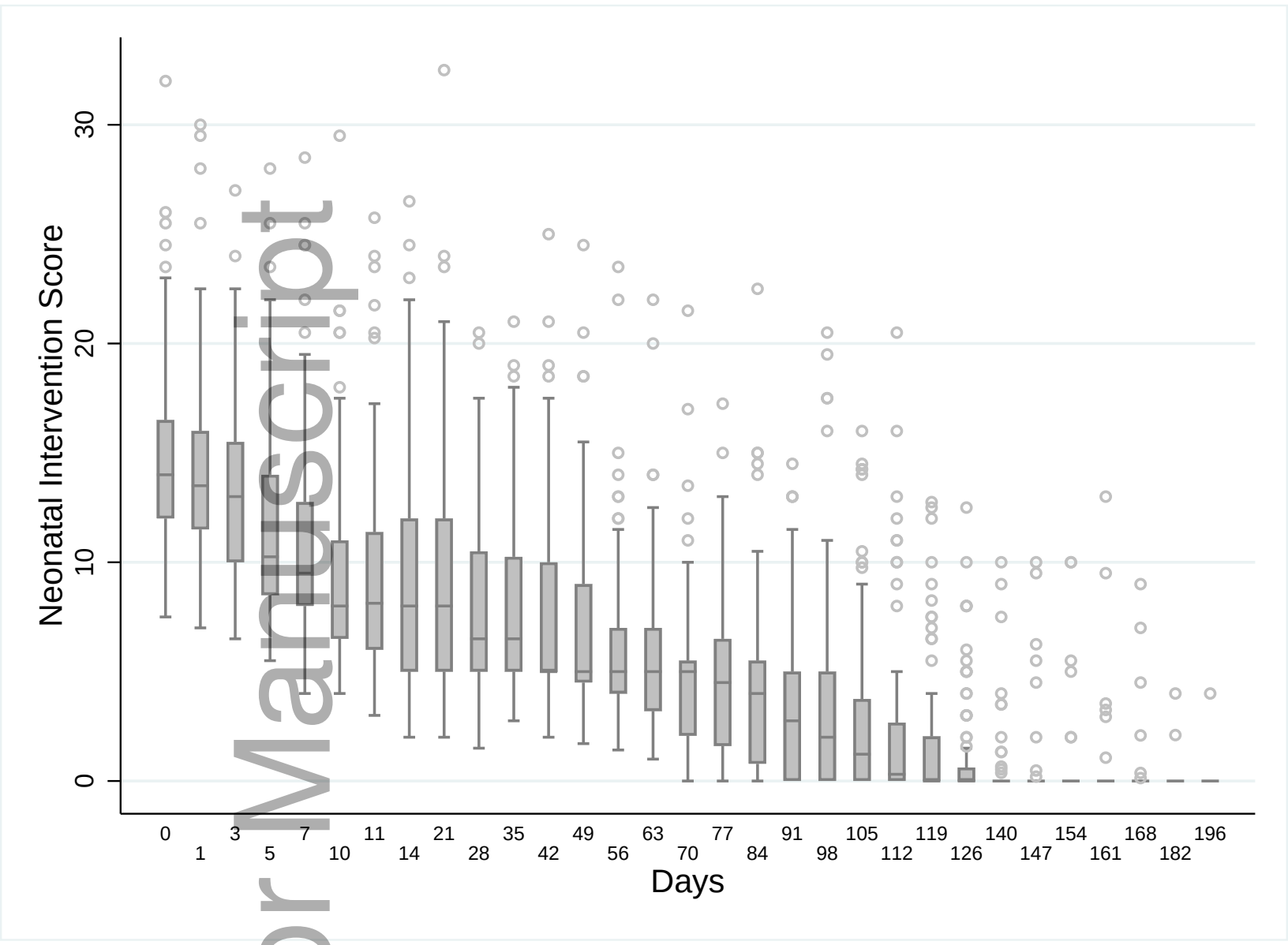

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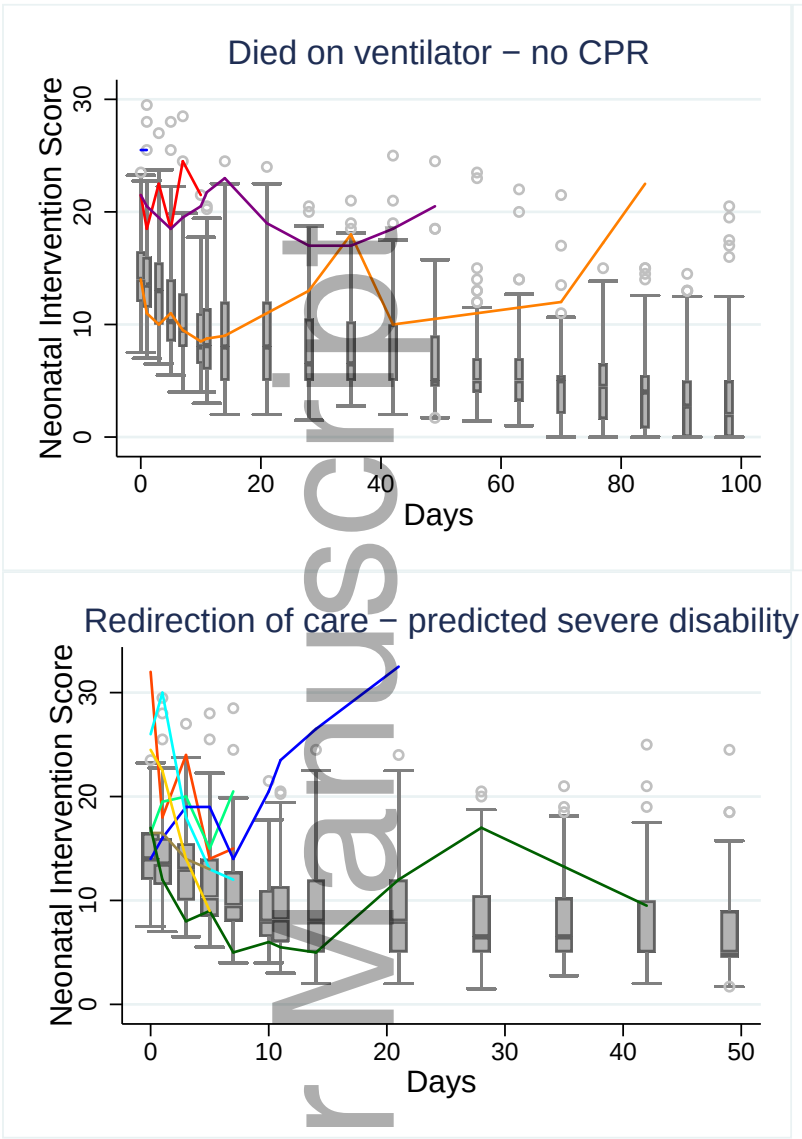

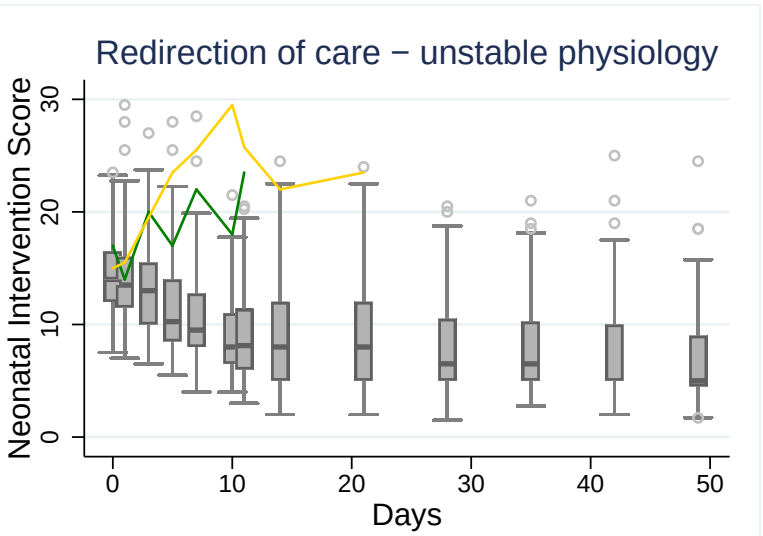

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