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Development and internal validation of a clinical prediction model for the needed level of care in preterm neonates

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Abstract

Purpose To address capacity problems at tertiary-level neonatal intensive care units (NICUs) within current staffing limitations, our study aims to demonstrate the feasibility of identifying very preterm neonates not in need of highly specialised, tertiary-level, NICU care.

Methods We developed and internally validated a clinical prediction model to identify very preterm neonates in need of tertiary-level NICU care within the first 72 h after birth in the Netherlands. The outcome was defined as one or more of: 1) endotracheal surfactant administration, 2) endotracheal/mechanical ventilation, and 3) inotropic administration. Multivariable logistic regression, with a priori selected predictors, was used on a retrospective cohort of very preterm neonates admitted to the tertiary-level NICU of Erasmus MC Sophia Children's Hospital, between January 2018 and December 2022. Bootstrapping was used for internal validation.

Results Of 654 included neonates, 45.1% ($n = 295$) needed tertiary-level NICU care. The final model included six predictors. Evaluating the model's discriminative performance resulted in an area under the receiver operating characteristics (ROC) curve of 0.77 [95%CI: 0.73–0.80]. A low-risk classification threshold of 20% yielded high sensitivity (93% [95%CI 90–96%]) and a specificity of 26% [95%CI: 22–31%], predicting a low risk of needing tertiary-level NICU care for 114 neonates, accurately selecting 94 of them.

Conclusion This prediction model demonstrates the feasibility of perinatal identification of very preterm neonates not in need of tertiary-level NICU care. Future research should focus on updating the model to a source population of women with imminent preterm birth.

Keywords Neonate, Premature, Neonatal intensive care units, Risk prediction, Location of birth

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Introduction

Hospital capacity strain, primarily caused by shortages of medical personnel, is one of the most urgent problems in neonatal healthcare nowadays [1, 2]. Staffing shortages are common at Neonatal Intensive Care Units (NICUs) due to the highly specialized nature of the work and given the emotional and psychological burden on healthcare professionals while caring for (extremely) premature and vulnerable neonates [3, 4]. Consequently, retaining current staff and the recruitment for specialized NICU nurses has proven to be difficult, with persistent job vacancies [5]. Capacity shortages at NICUs results in the inability to provide local care to all neonates in need of NICU admission, leading to antenatal maternal and postnatal neonatal transfers to alternative NICUs, far away from home and sometimes even across borders [6]. These transfers cause different types of problems, including medical risks, stress for pregnant women, their partners and their neonates, and substantially higher healthcare costs [7]. Altogether, these problems underscore the need to address capacity issues in neonatal care.

Neonatal care guidelines vary internationally, with different admission indications, in particular for the group neonates born between 28 + 0 and 31 + 6 weeks of gestational age (very preterm neonates), and definitions of care levels [8–12]. A commonly used subdivision is defined by the American Academy of Pediatrics classifying NICUs as NICU-levels I to IV, in order of increasing intensity and specialization of care [9]. In the United States and the Netherlands, very preterm neonates are typically allocated to highly specialised, tertiary, level-III NICUs, while in the United Kingdom and Sweden, they are primarily admitted to level-II NICUs; specialised neonatal wards [10]. These contrasting guidelines raise the question of whether very preterm neonates truly require tertiary-level NICU care for optimal outcomes [8, 13].

Moreover, some studies show that admissions to tertiary-level NICUs for non-acute very preterm neonates have been associated with poorer outcomes [14–18], possibly due to overmedicalisation [8], the impact of postnatal transfers to lower level facilities on the physiological stability [19], and high stress levels experienced by neonates and their caregivers triggered by the NICU environment and transfers. Given that very preterm neonates account for a substantial proportion of neonatal admissions [20], the neonatal care capacity strain further supports the importance of specialised level-II NICUs providing care for very preterm neonates [21, 22]. However, it remains unclear which neonates specifically benefit from this specialized level-II care and which neonates are in need for tertiary-level NICU care. Selecting those preterm neonates not in need of tertiary-level NICU be born in a level-II facility is essential, especially since postnatal transfers to a higher level NICU also come with medical risks [23]. Additionally, it is important to recognize that these outcomes are strongly influenced by country-specific care practices.

In the Netherlands, nine tertiary-level NICUs provide high acuity care for neonates, supported by affiliated hospitals with either high care neonatal (HCN), units that provide specialized neonatal care, or neonatal units that offer standard neonatal care. Each hospital has a maternal obstetric care unit corresponding to the neonatal level of care. Nationwide guidelines recommend preterm neonates with an estimated fetal weight below 1250 g or gestational age before 32 weeks to be born in a hospital with a tertiary-level NICU. Procedures such as surfactant administration, mechanical ventilation, inotropic administration, and therapeutic hypothermia are reserved for tertiary-level NICUs, making them comparable to the AAP-defined level-III NICUs. Specialized, HCN units, comparable to AAP-defined level-II NICUs, are staffed by personnel trained at a tertiary-level NICU, ensuring 24/7 availability of HCN nurses and an on-call neonatologist. These HCN units provide care for preterm neonates after their admission to a tertiary-level NICU, and preterm neonates born with a gestational age above 32 weeks.

Previous studies have examined risk factors for specific NICU-level III interventions, such as endotracheal surfactant administration [24, 25]. However, predictive factors for the required level of care as a whole remain unexplored [8]. Knowledge of the necessary level of care needed after birth, could prevent antenatal and postnatal transfers, potentially alleviating capacity issues and possibly improving patient outcomes. Therefore, our research aims to demonstrate the feasibility of perinatal identification of preterm neonates born between 28 + 0 and 31 + 6 weeks of gestational age, who do not require tertiary-level NICU care in the first 72 h after birth. To achieve this, we developed and internally validated a clinical prediction model for very preterm neonates in the South-West region of The Netherlands (consisting of one tertiary-level NICU, four specialized HCN units and six neonatal units), serving as an illustrative case study due to its urgent capacity issues [2, 12].

Methods

Participants

To be eligible to participate in this study, a subject met the following criteria:

- Gestational age between 28 + 0 and 31 + 6 weeks.
- Admitted to the Erasmus MC tertiary-level NICU between January 1st 2018 and December 28st 2022.
- Tertiary-level NICU admission within the first 72 h after birth.

A potential subject with a congenital anomaly with an indication for tertiary-level care, e.g. (major) cardiac defects or congenital diaphragmatic hernia, was excluded from participation. Other strict admission criteria for tertiary-level NICU care, aside from gestational age < 32 weeks and estimated fetal weight < 1250 g, are lacking. Therefore, we conducted a consensus survey among 24 health care providers in the Southwest region of the Netherlands, in order to specify our definition of tertiary-level NICU care (Supplemental File 1), and what care potentially could be provided in lower level care hospitals. It was deemed that neonates with an expected birth weight of < 1000 g need tertiary-level NICU care, therefore these subjects were excluded.

Source of data

At the tertiary-level NICU of the Erasmus MC-Sophia Children's hospital in Rotterdam in the Netherlands, medical data of admitted neonates was collected for healthcare evaluation purpose from electronic health records, creating a retrospective cohort. Data consisted of maternal background variables, pregnancy and delivery characteristics, and information on neonatal diagnoses, given treatments, and outcomes. Data was aligned with, but more extensive than, the Netherlands Perinatal Registry [26]. Data was de-identified before access was granted to the researchers.

Outcome definition

The outcome tertiary-level NICU care was defined as one or more of the following: 1) endotracheal surfactant administration, 2) endotracheal/mechanical ventilation, and 3) inotropic administration. This definition was based on the previously described survey (Supplemental File 1). The outcome was demarcated to 72 h after birth.

Predictors

A priori selected candidate predictors were based on expert clinical input, prior studies on the risk for neonatal respiratory disease [24, 27–30]. Since the prediction model is intended to be used perinatally, only the following perinatal known variables were selected: gestational age determined by first trimester ultrasound, estimated fetal weight, fetal sex, antenatal steroid administration, prolonged rupture of the membranes, maternal hypertension, magnesium administration, maternal fever, multiple pregnancy, and delivery mode (Supplemental File 2). We used birth weight as proxy for estimated fetal weight as this was unavailable in our dataset.

Sample size

A minimum sample size of 400 was advised based on an estimated 10 predictor variables [31] and an outcome incidence of 40% based on our own data and literature [24, 25].

Data preparation

Data was digitally recorded by the treating neonatologist directly after discharge. To minimize misclassification errors and/or typos a second person checked collected data for correctness. Data on treatments and diagnosis were registered as yes/no. For this specific study we also collected the timing after birth of the treatments defining NICU-care, using electronic patient records. Birthweight was converted to percentiles on the Fenton curve, using the PediTool package in R with the Fenton 2003 curves. Missing data was completed with the electronic patient records, with the exemption of one case where the preterm premature rupture of membranes (PPROM) status was not retrieved.

Statistical analysis

Model development was performed taking current methodological standards and the TRIPOD statement into account [31–33]. Logistic regression was used for univariate analysis and multivariate model development. Descriptive characteristics were analysed for the group with, and without need for tertiary-level NICU care with the Chi-Squared test for proportions and categorical variables, the independent t-test for continuous data, and the Mann-Whitney U test for skewed data. For continuous variables, linearity in the logit was checked and challenged by categorisation, splines, and fractional polynomials. For predictor selection, a full model approach with complete cases was used, removing predictors with a p-value > 0.2 automatically.

Calibration was evaluated with a calibration-in-the-large graph and the Homers-Lemeshow test. Outliers were identified by calculating influence and biologically checked. Model performance was evaluated using a Receiver Operating Characteristics(ROC)-curve with area-under-the-curve (AUC). Bootstrapping with 500 replications, using the validate() function from the rms package, was used to internally validate the model and present an optimism corrected AUC. Furthermore, an overview of sensitivity, specificity, and negative likelihood ratios at different threshold percentages were calculated to provide insight in clinical impact of the prediction model. The model development and validation steps were repeated for the subset of cases with completed steroid course and for the subset of preterm neonates with gestational ages between 30 + 0 and 31 + 6 weeks, since we expected the number of neonates not in need of tertiary-level NICU care to be proportionally the largest for these subgroups. Also, a sensitivity analysis was performed without the predictors 'delivery mode' and 'magnesium', as these

predictors could be unknown at time of maternal admission to a hospital. Statistical analysis was performed using R-studio version 2022.07.2 and statistical code is provided in Supplemental File 3.

Patient and public involvement statement

Parents were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Of 3099 neonates admitted to the Erasmus MC tertiary-level NICU between January 1st 2018 and December 31st 2022, 819 were very preterm neonates (gestational age 28 + 0–31 + 6 weeks). Of these, 25 were excluded based on congenital abnormalities, 48 because they were admitted later than 3 days of life, and 92 had a birthweight < 1000 g (Supplemental File 4). Population demographics are shown in Table 1. Overall, 45.1% of included patients received tertiary-level NICU care ($n = 295$). As expected, this proportion decreased with increasing

Table 1 Descriptive characteristics

Characteristic	Not in need of tertiary-level NICU care < 72 h after birth	In need of tertiary-level NICU care < 72 h after birth	Statistics*
	N = 359	*N* = 295	
Female	155 (43.2%)	122 (41.4%)	$p = 0.639$
Birthweight (gram)	1480 [1260–1660]	1410 [1208–1610]	$p = 0.0497$
Fenton Percentile (percentile)	53.8 [37.5–71.1]	58.9 [41.0–75.1]	$p = 0.0237$
Gestational age (weeks + days)	30 + 5 [29 + 4–31 + 2]	30 + 0 [29 + 0–30 + 6]	$p < 0.0001$
Multiple pregnancy	100 (27.9%)	69 (24.4%)	$p = 0.194$
Delivery mode (C-section)	199 (55.4%)	215 (72.9%)	$p < 0.0001$
Outcomes			
Mortality	3 (0.8%)	21 (7.1%)	$p < 0.0001$
Sepsis (blood culture positive)	27 (7.5%)	38 (12.9%)	$p = 0.023$
Early onset (< 72 h after birth)	2 (0.6`%)	12 (4.1%)	$p = 0.007$
Late onset (> 72 h after birth)	25 (7.0%)	26 (8.8%)	$p = 0.667$
NEC	11 (3.1%)	4 (1.4%)	$p = 0.147$
IVH gr 3	4 (1.1%)	10 (3.4%)	$p = 0.041$
Convulsion	0	6 (2.0%)	$p = 0.007$
Asphyxia[Y]	0	15 (5.1%)	$p < 0.0001$
Length of stay at the tertiary-level NICU (days)	5 [3–11]	10 [6–17]	$p < 0.0001$
Components of tertiary-level NICU care			
Surfactant	-	264 (89.5%)	#
Mechanical ventilation	16 (4.5%)	152 (51.5%)	$p < 0.0001$
<72 h after birth	-	146 (49.5%)	#
Inotropic administration	6 (1.7%)	42 (14.2%)	$p < 0.0001$
< 72 h after birth	-	36 (12.2%)	#
Maternal characteristics			
PPROM[$]	120 (33.4%)	51 (17.3%)	$p < 0.0001$
Antenatal corticosteroids administered			$p < 0.0001$
No dose	26 (7.2%)	78 (26.4%)	
1 dose	77 (21.4%)	73 (24.7%)	
2 doses	256 (71.3%)	144 (48.8%)	
Maternal fever	16 (4.5%)	16 (5.4%)	$p = 0.568$
Maternal hypertension	48 (13.4%)	65 (22.0%)	$p = 0.004$
Magnesium administration	261 (72.7%)	148 (50.2%)	$p < 0.0001$

Categorical data are presented as frequency (%), continuous data were skewed and presented as median [75% IQR]

Abbreviations: *C-section* caesarean section, *NEC* necrotizing enterocolitis (Bells stadium IIa, IIb, or III), *IVH* intraventricular haemorrhage (classification according to Papile et al.), *PPROM* preterm prolonged rupture of the membranes

*Proportions and categorical variables were compared using the Chi-Squared test. Continuous variables were all skewed and compared using the Mann-Whitney U test

[Y]Asphyxia yes/no as defined by Cowan et al

#Chi-Squared tests were not performed, since these variables were criteria for the need for tertiary-level NICU care and per definition not present in the group without need for tertiary-level NICU care

[$]one missing value for the variable PPROM. All other variables had no missing data

gestational age (Fig. 1). Respiratory treatments, surfactant administration and mechanical ventilation, contributed 98.6% ($n = 291$) to the need for tertiary-level NICU care.

Model derivation and performance

Univariate logistic regression (Table 2) showed that increasing gestational age, PPROM, completed antenatal steroids course, and magnesium administration reduced the odds for the need of tertiary-level NICU care. Increasing Fenton percentile, maternal hypertension, and caesarean section were risk factors. Sex, maternal fever, and multiple pregnancy were excluded from multivariable predictor selection. Natural splines for gestational age had a slightly better fit ($p = 0.048$), but for simplicity reasons a linear coefficient was used.

Model calibration was good, with a Hosmer-Lemeshow test of 0.85 (Calibration-in-the-large Graph is presented in Supplemental File 5). Influential subjects ($n = 6$) were biologically plausible. The model's discriminative ability resulted in an AUC of 0.77 (95%CI: 0.73–0.80, internal bootstrap validation: 0.75)(Fig. 2). Subgroups and sensitivity analyses showed comparable results (Supplemental File 6).

Threshold determination

The influence of different low-risk, rule-out, thresholds is presented in Table 3. For example, using a low-risk threshold of 20%, corresponding with a negative likelihood ratio of 0.26, resulted in 114/654 neonates with a predicted low risk of needing tertiary-level NICU care, accurately selecting 18.8 neonates a year without need for tertiary-level NICU care. On the other hand, 20 out of 114 low-risk classified neonates were in need of tertiary-level NICU care and would need back transport to the tertiary-level NICU.

Discussion

In a Dutch study population, we developed and internally validated a clinical prediction model. This model aims to identify very preterm neonates (28 + 0 to 31 + 6 weeks gestational age) not in need of tertiary-level NICU care within 72 h after birth. Using perinatal predictors, the model showed good calibration and discrimination (AUC 0.77). A rule-out threshold of 20% yielded a high sensitivity (93%) and negative predictive value (85%), demonstrating the feasibility of perinatal identification of level of care directly after birth. This study is a necessary first step towards optimizing neonatal capacity allocation.

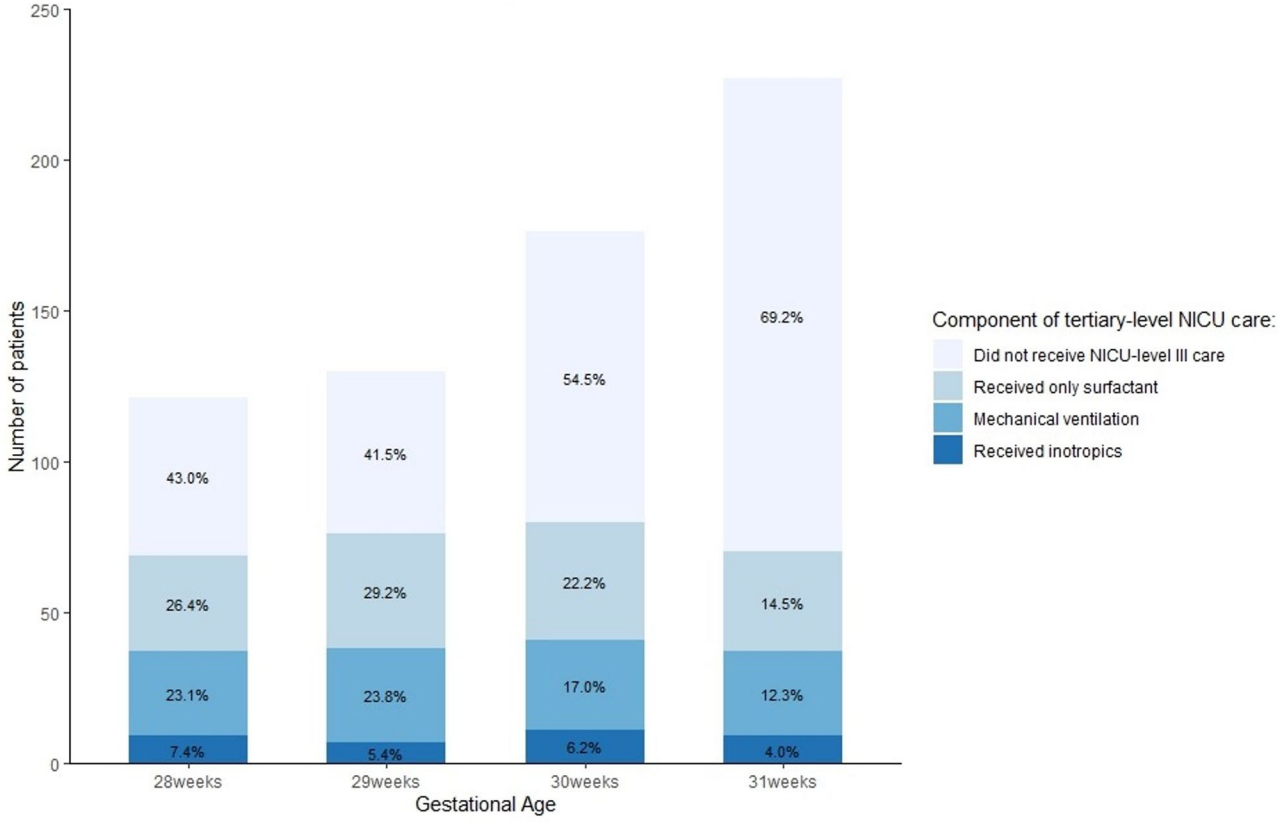

Fig. 1 Components of tertiary-level NICU care per gestational age week. Percentages represent the proportion of neonates needing a component of tertiary-level NICU care in that specific gestational age week

Table 2 Candidate predictors of the need for tertiary-level NICU care for very preterm neonates

Variable	Univariate	Multivariate	
	Odds Ratio [95% CI]	Estimated Coefficient	Odds Ratio [95% CI]
Intercept	-	0.595	1.812 [0.818–4.045]
Sex (female)	0.928 [0.679–1.268]	-	-
Gestational Age (weeks)*	0.691 [0.601–0.793]	−0.452	0.636 [0.543–0.743]
Fenton percentile (1–100%)*	1.008 [1.002–1.015]	0.013	1.013 [1.004–1.022]
PPROM*	0.415 [0.284–0.599]	−0.502	0.605 [0.394–0.924]
Antenatal steroids (yes)	0.384 [0.277–0.529]	−0.923	0.397 [0.269–0.582]
Maternal hypertension*	1.831 [1.218–2.770]	1.330	3.782 [2.186–6.654]
Maternal magnesium*	0.378 [0.272–0.522]	−0.952	0.386 [0.262–0.566]
Maternal fever	1.229 [0.600–2.519]	-	-
Multiple pregnancy	0.791 [0.553–1.126]	-	-
Delivery Mode (C-section)*	2.161 [1.557–3.016]	0.788	2.199 [1.497–3.253]

Abbreviations: *C-section* caesarean section, *PPROM* preterm prolonged rupture of the membranes

* Predictors with a *p*-value < 0.2 for univariate logistic correlation

Comparison with literature

Our study found that 45.1% of very preterm neonates (36.7% for 30 to 31 + 6 weeks) required tertiary-level NICU care, contributing to the discussion about the appropriate location of care for these neonates [13, 18]. Differences in organisation of care challenge this discussion and the interpretability of findings.

In the absence of models predicting overall neonatal care needs, we compared our model to literature focussing on specific neonatal outcomes, term infants, and postpartum predictors. Consistent with literature, increasing gestational age, PPROM and completed steroids course reduced risk of tertiary-level NICU care, while caesarean section increased it [30, 34–40]. PPROM reduce risk possibly due to chorio-amnionitis associated acceleration of maturation of fetal lung tissue, diminishing the need for surfactant and mechanical ventilation [41–43]. The unexpected risk associated with higher Fenton percentile [44] may reflect our exclusion of neonates under 1000 g, including only 18 (2.8%) neonates with a Fenton percentile < 10%. Also, spontaneous preterm birth in between 30 and 32 weeks of gestation occasionally occurs affiliated hospitals unplanned. When doing well these neonates remain in the affiliated hospital while those with need of tertiary-level care are admitted to

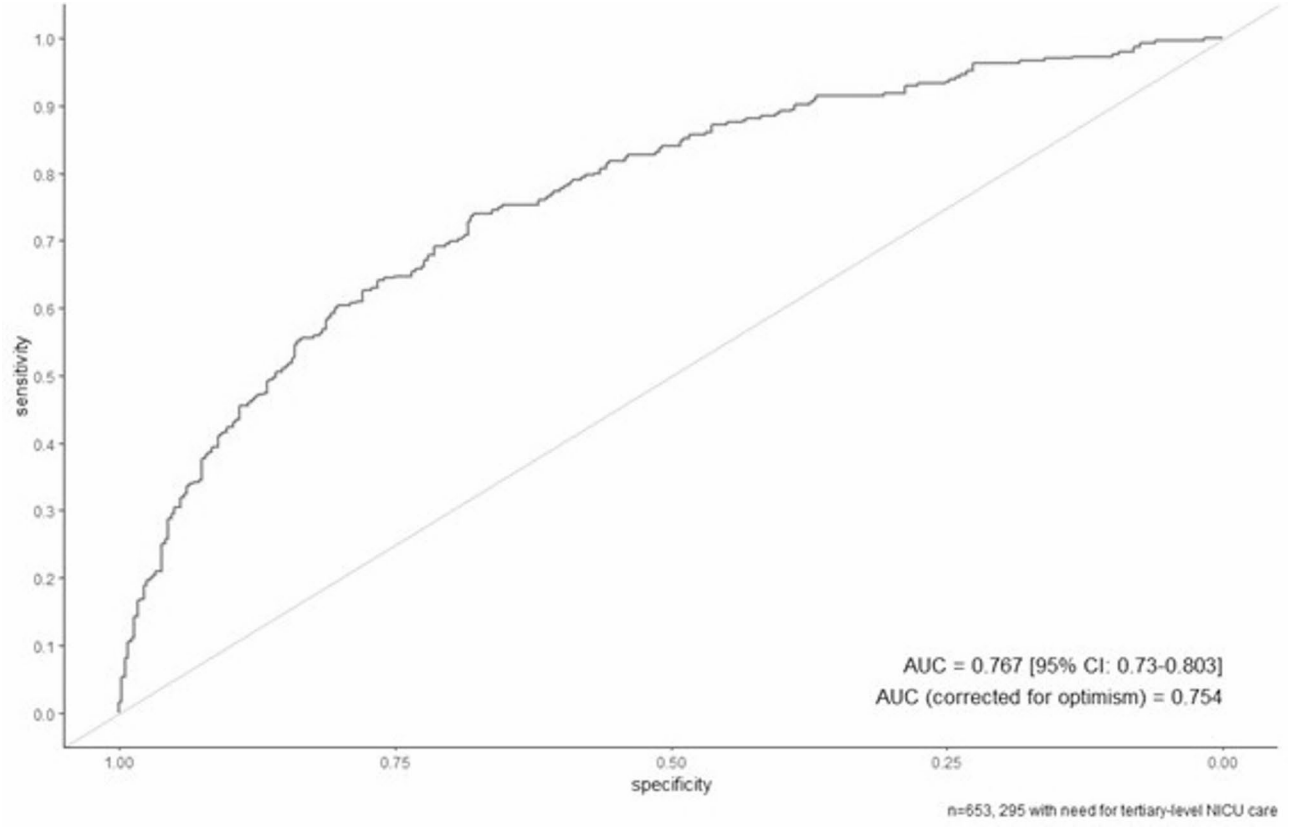

Fig. 2 Receiver Operating Characteristics Curve

Table 3 Characteristics of the multivariate prediction model, presented for different classification thresholds

Test characteristics				Patients classified as low risk		Patients classified as high risk	
Threshold	Sensitivity % [95% CI]	Specificity % [95% CI]	Negative Likelihood Ratio [95%CI]	Patients without need for tertiary-level NICU care (*n*)	Patients with need for tertiary-level NICU care (*n*)	Patients without need for tertiary-level NICU care (*n*)	Patients with need for tertiary-level NICU care (*n*)
< 10%	99 [98–100]	6 [4–9]	0.11 [0.03–0.44]	23	2	335	293
< 15%	97 [94–99]	16 [12–20]	0.19 [0.10–0.38]	57	9	301	286
< 20%	93 [90–96]	26 [22–31]	0.26 [0.16–0.41]	94	20	264	275
< 25%	90 [86–93]	37 [32–43]	0.27 [0.18–0.38]	134	29	224	266
< 30%	87 [83–91]	46 [41–52]	0.28 [0.20–0.38]	166	38	192	257
< 35%	83 [78–87]	53 [47–58]	0.33 [0.25–0.43]	187	51	171	244

the tertiary-level NICU. This may have introduced bias as neonates from mothers with hypertensive disorders rarely give birth in affiliated hospitals but have lower Fenton percentiles. Contrary to existing studies [45], magnesium appeared protective, possibly due to unmeasured confounders.

Strengths and limitations

To the best of our knowledge, this is the first study to predict overall needed level of neonatal care, using a large study population. We used high quality data derived with very low number of missing data, due to structured data collection in the Netherlands Perinatal Registry. Furthermore, aligning the outcome definition and predictors the obligatory Netherlands Perinatal Registry increases generalizability [26].

However, limitations include the data source, absence of predictor timestamps, single-centre design, and lack of real-world data from HCN units. First, the use of a source population consisting of neonates rather than pregnant women, implies that the data does not perfectly align with the application of the prediction model. We used birth weight as proxy for estimated fetal weight, justified by high accuracy of modern ultrasound models to estimate fetal weight [46]. Also, at the intended moment of use, when a pregnant woman presents with imminent preterm birth, there is uncertainty about whether the baby will be born [47, 48]. We acknowledge these limitations and recommend using a rule-out/low-risk threshold with high sensitivity. Potential biases tend towards conservation predictions, likely minimizing medical risks for neonates.

Second, the collected data did not include time stamps, while the risk prediction likely changes over time due to the evolving status of predictor variables (corticosteroids, magnesium, planned delivery mode). One potential solution is to recalculate the prediction periodically after admission. In clinical practice, this could lead to mothers with imminent preterm birth initially being admitted to a hospital with tertiary-level NICU care, as predicting variables are not yet assessed or available. Subsequently, after assessing the predicting variables and potentially using observation time to complete corticosteroids, the risk of needing tertiary-level NICU care decreases below a given threshold, and mothers might be transferred to another hospital for potential delivery.

A third limitation is the single-centre design of the study. While nationwide protocols aim to standardize treatment strategies for surfactant administration, mechanical ventilation, and non-invasive respiratory treatment, centre-specific variations in treatment strategies can affect external validity and therefore the generalizability. To prevent overfitting of the model, we used bootstrapping with internal validation. Nevertheless, a multi-centre validation study is a pivotal next step.

Last, ensuring similar quality of perinatal care for selected mothers and neonates, potentially treated in HCN units, is essential. Nationwide protocols are applicable to both tertiary-level NICUs and HCN units, and training programmes for medical teams in the HCN units are obligatory and facilitated by the tertiary-level NICU. Despite these efforts, the need for mechanical ventilation might be more frequent when born in HCN units due to less frequent exposure. Possible redesign of perinatal care must therefore be accompanied by training programmes and close monitoring of perinatal outcomes.

Clinical implications

Despite variations in NICU admission criteria and the specificity of our outcome definition, our study serves as a proof of concept for perinatal prediction of neonatal care needs. A few essential steps need to be undertaken, starting with external validation and model updating in a multicentre cohort. Once externally validated, the

prediction model in its currents form and in the current healthcare system, has the potential to identify pregnant women that can be transferred back to a hospital with HCN unit after initial evaluation and management in a tertiary-level hospital. The risk for tertiary-level NICU care decreases after an initial observation period, facilitating this transfer opportunity increasing obstetric capacity in the tertiary-level hospital for a clinically relevant number of women.

Subsequently, updating the model to a cohort of women with imminent preterm labour including time series of predictor variables is needed to identify pregnant women on initial assessment for imminent preterm birth. Additionally, focus groups can efficiently help to define the optimal low-risk threshold and determine the acceptable number of extra transfers from high care neonatal units to tertiary-level NICUs. We also advise performing an impact estimation of the model on the number of deliveries and admission days in HCN and obstetric units, to align expected obstetric and neonatal capacity of hospitals with their current bed capacity and ensure a smooth implementation in a clinical trial [49].

Conclusion

This study showed that approximately half of the very preterm neonates admitted to the tertiary-level NICU did not require tertiary-level NICU care did not meet our definition of tertiary-level NICU care. Those patients may therefore be appropriate for a lower level of care, providing an opportunity to improve quality of care, avoiding transfers, and alleviate capacity strain and high healthcare costs. Our internally validated prediction model demonstrates the feasibility of perinatal identification of very preterm neonates not requiring tertiary-level NICU care, proving the first steps towards integrating prediction models into neonatal care allocation. Defining the clinical moment of use and performing a multi-centre external validation are pivotal next steps.

Abbreviations

AUC	Area Under the Curve
HCN	High Care Neonatal
NICU	Neonatal Intensive Care Unit
PPROM	Preterm Premature Rupture of Membranes
ROC	Receiver Operating Characteristics

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-06316-x.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

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Clinical trial number

Not applicable.

Authors' contributions

JW was responsible for conceptualization, methodology and interpreting of the results together with HRT. She supervised MB in data preparation, performed statistical analyses and was responsible for writing the original draft. AF and IR provided clinical input. AF, MK and IR assisted with the discussion of the results. All authors reviewed and critically revised the manuscript. All authors read and approved the final version of the manuscript. HRT is responsible for the overall content as guarantor.

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Data availability

Statistical code is available as supplemental file. Data is available upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was reviewed by the Medical Ethical Committee of the Erasmus MC with identification number: MEC-2023-0425. The need for informed consent was waived by the committee and they confirmed that the rules laid down in the Medical Research Involving Human Subjects Act (also known as the Dutch abbreviation WMO) do not apply.
Not applicable.

Competing interests

The authors declare no competing interests.

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