Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Running title: practices and morbidities, and outcomes in preterm infants

Abstract

Background: The interventions and incidences of morbidities among very-low-birth-weight (VLBW) infants vary between centers. If the center variation is very wide, the standardization of established treatment is a more pressing issue than the introduction of a new treatment by clinical trial. This study aimed to distinguish between clinical trials and standardization to further improve outcomes among VLBW infants.

Method: The study design was a retrospective observational analysis. This study included 15,920 VLBW infants from 2003 through 2010 from 38 participating hospitals in Japan. A multivariate logistic model identified practices and morbidities associated with mortality by adjusting for the background risk factors of the infants. The practices and morbidities that were significantly associated with mortality were then analyzed using a multilevel logistic model with the same risk adjustment. The residues calculated by the multilevel analysis were used as an indicator of center variation.

Results: Risk-adjusted odds ratios and center variations distributed with variable odds ratios and center variations. Among practices, antenatal steroids and intubation at birth showed relatively high center variations (0.9 and 0.8) and favorable odds ratios (0.7 and 0.5) for mortality, while Cesarean section showed a low center variation (0.4) and a favorable odds ratio (0.8). Sepsis and air leak showed high center variations (0.4 and 0.4) and high odds ratios (3.8 and 3.4) among morbidities. Pulmonary hemorrhage, persistent pulmonary hypertension of the newborn, and intraventricular hemorrhage showed moderate variations (0.2, 0.3, and 0.2, respectively) and high odds ratios (5.6, 4.1, and 2.9, respectively). In contrast, necrotizing enterocolitis showed the lowest variation (0.1) and a high odds ratio (4.9).

Conclusion: The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques. In contrast, standardization must be considered for practices and morbidities with a high center variation.

Article summary

Article Focus:

X: There exists a center variation in practices and incidences of morbidities among high risk infants.

X: If the center variation is wide, the standardization of established treatment is more important than the introduction of a new practice by clinical trial.

X: An analysis of network database may provide the necessity of clinical trial or standardization.

Key messages:

X: Risk-adjusted center variations of interventions and morbidities among high risk infants were calculated using a multilevel analysis.

X: The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques.

X: In contrast, standardization must be considered for practices and morbidities with a high center variation.

Strengths and Limiatations:

X: The strength of the study is that all analysis was derived from a large database.

X: The limitation of the study is that limited number of hospitals participated the study.

Key words: standardization, neonate, research network, variation, multilevel analysis

<Introduction>

Although there have been constant advances in neonatal care, there is still significant room to improve outcomes in very-low-birth-weight (VLBW) infants.[1–5] If some interventions or morbidities are strongly associated with outcomes, they should be improved through newly introduced treatments. However, it is also true that there is center variation in interventions and the incidences of morbidities.[6] Routine practices may vary even among level III neonatal intensive care units (NICUs). If this center variation is associated with increased mortality, the standardization of these practices is more pressing than the introduction of a new treatment for the improvement of outcomes of VLBW infants. Because the practices and morbidities in hospitals can be affected by both the relevance of risk and center variation, a two-dimensional approach using two multivariate logistic models was used in this study. The first dimension estimated the risk of an individual practice or morbidity in association with mortality using a linear logistic model by controlling for background risk factors. The second dimension evaluated the center variation in practices and morbidities using a multilevel logistic analysis including individual hospital as an independent variable. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques. In contrast, if the center variation is high, the standardization of established treatments among hospitals through the implementation of guidelines is more important than a newly introduced clinical trial. Thus, we speculated that this type of approach of two-dimensional plotting is useful for the improvement of patient outcomes.

<Subjects & Methods>

Study design

The study is an observational analysis of the neonatal database. All data were retrospectively analyzed.

Patient selection

A neonatal research network database in Japan was used in the present study. The database included infants with birth weights at or less than 1,500 g who were treated in participating neonatal centers. To characterize the risk of each practice or morbidity with mortality and their center variation among hospitals, 17,156 infants born from 2003 through 2010 at 38 hospitals that participated in the network throughout the 8 years were analyzed. Among all the infants, 33 infants died in the delivery room, and 1,168 infants with major congenital anomalies were excluded from the study because mortality in those infants was beyond the quality of NICU care. Furthermore, 35 infants were also excluded due to incomplete data registration. Thus, 15,920 infants were included in the study (Fig 1). All 38 hospitals were designated as level III perinatal centers. The definitions of the collected variables were as previously reported, and available on web (http://plaza.umin.ac.jp/nrndata/).[6]

Statistics

1) Identifying risk factors at birth for mortality

To identify risk factors at birth for mortality among VLBW infants, a linear logistic model was introduced using dead in the NICU as a dependent factor. The risk factors tested were

maternal age, primipara, multiple pregnancy, pregnancy-induced hypertension (PIH), diabetes mellitus, clinically diagnosed chorioamnionitis, fetal heart rate abnormalities (NRFS: non-reassuring fetal status), delivery presentation, mode of delivery, gestational age, birth weight, gender, and 1 min Apgar score. Independent variables of mortality were used in this model to adjust background risks of the infants for the following analyses.

2) Calculating odds ratios of practices and morbidities for mortality

To calculate the odds for mortality, another linear logistic regression model was established. In this model, all of the above variables that were independent risk factors for mortality were included. Furthermore, each practice or morbidity was included as an independent variable in the model. To evaluate positive risks for mortality, each practice and morbidity was converted to produce odds ratios more than 1.0, if necessary.

The hospital practices analyzed for association with mortality in the infants were antenatal steroids (ANSs), Cesarean section (C/S), neonatal transport, cord blood transfusion, oxygen use at birth, intubation at birth, continuous positive airway pressure, mechanical ventilation, high-frequency oscillatory ventilation, pulmonary surfactant, inhaled nitric oxide, indomethacin, patent ductus arteriosus (PDA) ligation, glucocorticoid for chronic lung disease (CLD), and intravenous alimentation.

The morbidities analyzed among the infants were respiratory distress syndrome (RDS), air leak syndrome, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn (PPHN), CLD at 28 days after birth, CLD at 36 weeks of corrected age, symptomatic PDA, late-onset adrenal insufficiency of prematurity, intraventricular hemorrhage (IVH), IVH grade

III/IV, periventricular leukomalacia, sepsis, and necrotizing enterocolitis (NEC)/intestinal perforation. All these variables were tested for their independent effect on mortality using a stepwise logistic analysis.

3) Calculating center variations

Another logistic model with multilevel analysis was applied to evaluate hospital variations in each practice and morbidity.[7] In this model, each practice and morbidity was included as a dependent variable. The residues calculated by the multilevel analysis, which indicate the difference in practice or the incidence of morbidities among the hospitals adjusted for background risks, were used as an indicator of center variations in NICUs for VLBW infants.

4) Statistical methods

All statistical analyses were performed using MLwiN version 2.2 (Center for Multilevel Modeling, University of Bristol, UK).

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

<Results>

1) Risk factors at birth for mortality

The multivariate logistic model showed that multiple pregnancy, PIH, CAM, NRFS, presentation of the fetus, mode of delivery, gestational age more than 37 or less than 24 weeks, birth weight, gender, and Apgar scores <4 at 1 min were considered significant independent variables associated with NICU mortality. These variables were used for adjusting the background risks of the infants for further analyses.

2) Risk-adjusted odds ratios of practices and morbidities and hospital variation

ANSs, C/S, and intubation at birth were practices that were significantly associated with mortality, while RDS, air leak, pulmonary hemorrhage, PPHN, IVH, sepsis, and NEC were morbidities significantly associated with mortality. Center variations were calculated for these practices and morbidities. Table 1 shows the odds ratios and center variations of each practice or morbidity with 95% confidential intervals.

3) Two-dimensional plotting

Figures 2 and 3 show the two-dimensional distribution of odds ratios for mortality and center variations. Among practices, ANSs and intubation at birth showed relatively high center variations and favorable odds ratios for mortality, while C/S showed a low center variation and the same favorable odds ratio. Sepsis and air leak showed high center variations and high odds ratios for mortality among morbidities. Pulmonary hemorrhage, PPHN, and IVH showed moderate variations and high odds ratios. In contrast, NEC showed the lowest variation, with a high odds ratio.

<Discussion>

The two-dimensional approach described here clearly distinguished between the standardization of established treatments and the introduction of new treatment for the further improvement of outcomes among VLBW infants. If there is a wide center variation in practices or morbidities, standardizing current practices or preventing morbidities must be considered first. In contrast, if the center variation is small, a new intervention for improvement needs to be tested.

ANSs and intubation at birth were among practices that had a less than 1 odds ratio for mortality and a high center variation. For these practices, standardization should be introduced for improvement. Specifically, the benefit of ANSs is already well proved. Thus, the standardization of this practice would not be difficult. Intubation at birth seems to be favorable for saving VLBW infants. However, the beneficial effect on morbidities, such as CLD and retinopathy of prematurity, must be considered from a different point of view. C/S showed an odds ratio less than 1 and low center variation. Thus, a clinical trial to demonstrate the efficacy of C/S when delivering VLBW infants is necessary before it is used as a routine practice.

Among morbidities, sepsis and air leak showed high center variations and high odds ratios for mortality. It would be difficult to introduce a new intervention to reduce these morbidities before standardizing daily practices in NICUs. If some NICUs with these high morbidities can change their routine practices to reduce their incidence, it may be more effective rather than to develop new treatments. IVH, PPHN, and pulmonary hemorrhage had high odds ratios for mortality. However, their center variations were moderate. For these

morbidities, standardization and the development of new treatment will be essential. In contrast, the odds ratio of NEC was high, while its center variation was the smallest among the morbidities. This result indicates that new treatment is necessary to reduce this morbidity.

We have often experienced that the introduction of a newly invented intervention with a high expectancy failed to prove its efficacy in a clinical trial. In this case, wide center variation might compromise the benefit of the intervention. The importance of surveying center variation was previously reported.[8] Furthermore, center variation actually impaired several important clinical trials.[9,10] We believe that our analysis can answer the question of which comes first, clinical trial or standardization.

The limitation of this study is that the analysis was performed only among 38 hospitals, and therefore, the tendency shown in the study does not reflect a nationwide trend. However, these hospitals are leading NICUs, and covering 30% of total VLBW infants born in Japan. Thus, the center variations among these NICUs are hypothesized to be the smallest in Japan. If we included all NICUs in the country, we would have observed wider center variations. We believe that the analysis of a limited number of hospitals is appropriate for this type of study. Additionally, the database does not include information about the timing of morbidities. Thus, a separate time to event analysis on each morbidity is necessary.

In conclusion, the simultaneous evaluation of the risks and the center variations in practices or morbidities are useful to find the new strategy for the further improvement of outcomes in VLBW infants. This kind of approach is also reasonable and important in another field of medicine, if there is the probability of center variations in practices and morbidities.

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Figure legend

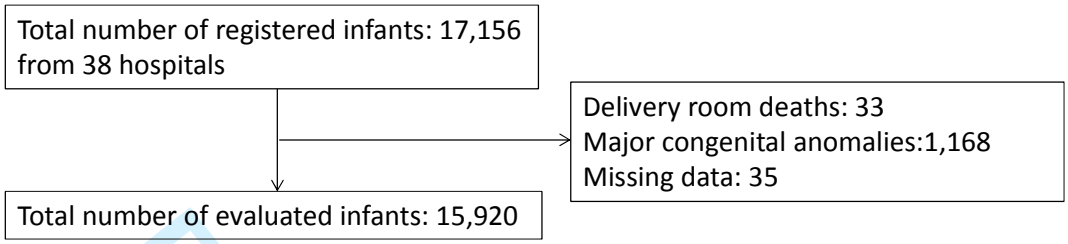


Fig. 1 Flowchart of registration and evaluation

Total 17,156 infants whose birth weight at or less than 1500g were registered on the database. Among them, 33 infants with delivery room death regardless of vigorous resuscitation, 1,168 infants with major congenital anomalies, and 35 infants with incomplete registration were excluded from the study.

Thus, the number of infants evaluated was 15,920, which were reported from 38 hospitals during the study year 2003 through 2010.

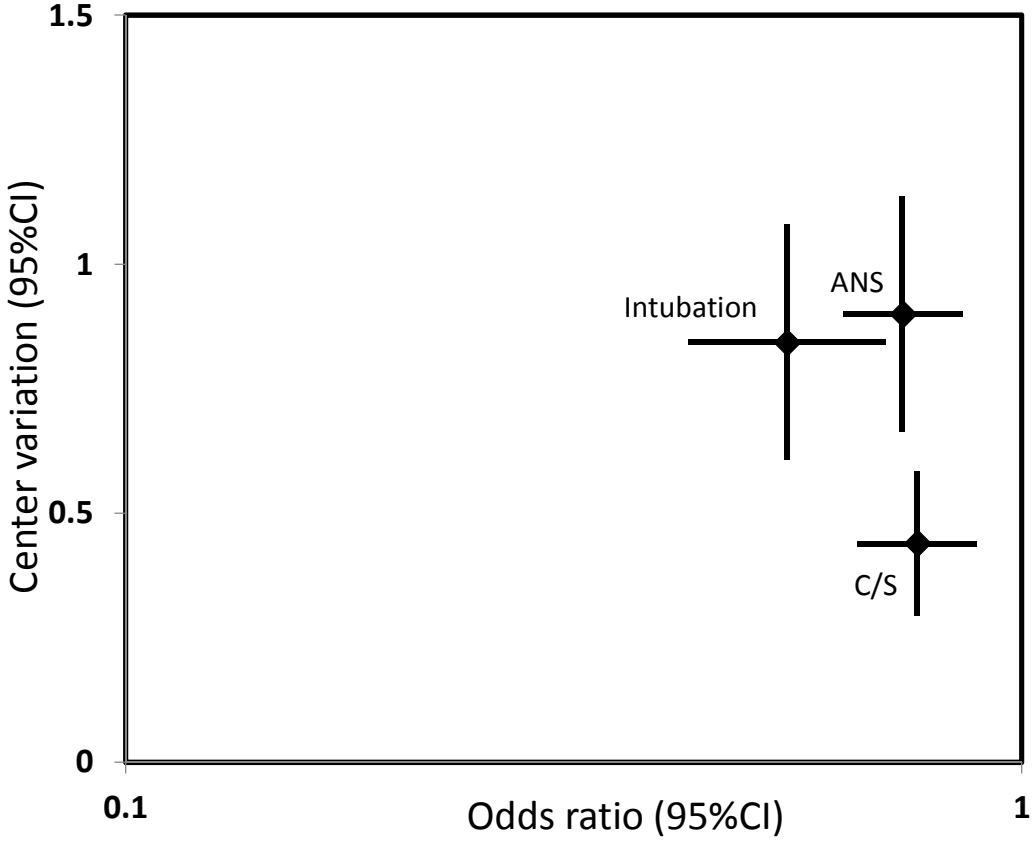


Fig. 2 Distribution of odds ratios for mortality and center variations in practices

The x-axis shows risk-adjusted odds ratios of each practice for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each practice among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

ANSs: antenatal steroids, Intubation: resuscitation with intubation at birth, C/S: Cesarean section

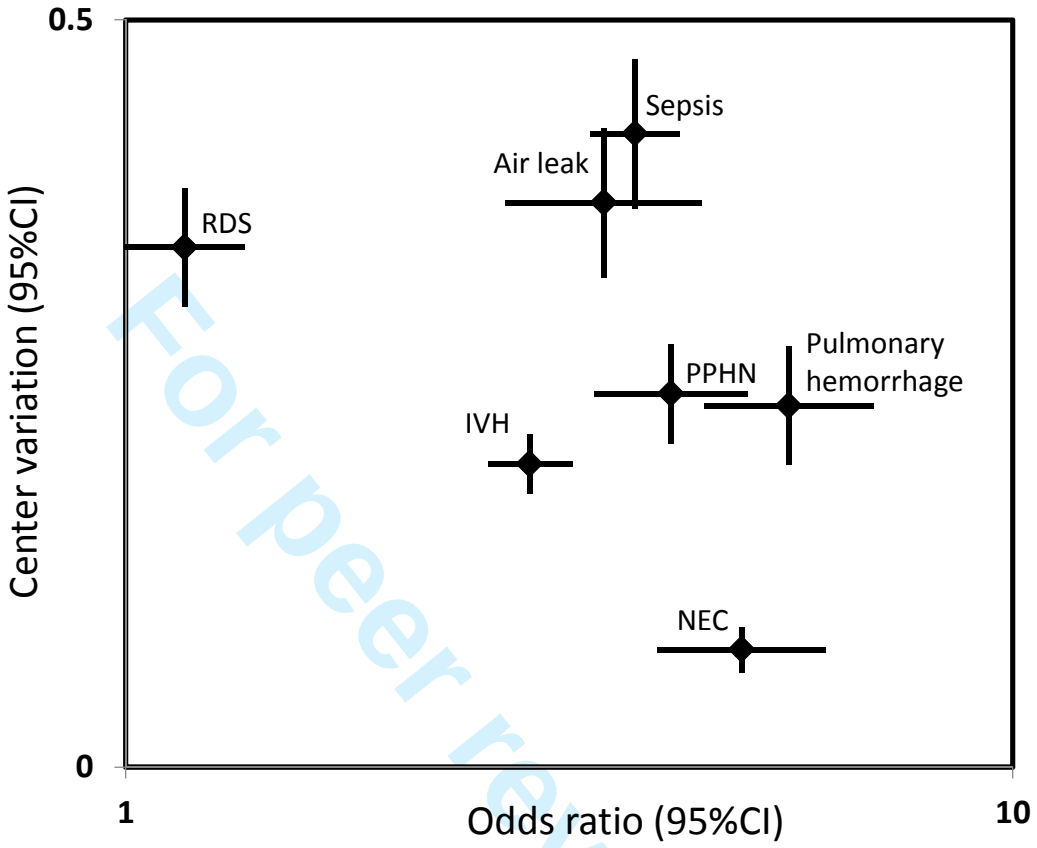


Fig. 3 Distribution of odds ratios for mortality and center variations in morbidities

The x-axis shows risk-adjusted odds ratios of each morbidity for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each morbidity among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome

Table

Table Odds ratios and center variation among practices or morbidities

Practice/Morbidity	Odds ratio (95%CI)		Center variation (95%CI)	
Practice				
ANS	0.7	(0.6–0.9)	0.9	(0.5–1.3)
C/S	0.8	(0.7–0.9)	0.4	(0.2–0.6)
Intubation	0.5	(0.4–0.7)	0.8	(0.5–1.2)
Morbidity				
RDS	1.2	(1.0–1.4)	0.3	(0.2–0.5)
Air leak	3.4	(2.7–4.5)	0.4	(0.2–0.6)
Pulmonary hemorrhage	5.6	(4.4–6.9)	0.2	(0.1–0.4)
PPHN	4.1	(3.4–5.0)	0.3	(0.1–0.4)
IVH	2.9	(2.5–3.3)	0.2	(0.1–0.3)
Sepsis	3.8	(3.2–4.4)	0.4	(0.2–0.6)
NEC	4.9	(3.9–6.2)	0.1	(0.0–0.2)

ANSs: antenatal steroids, C/S: Cesarean section, Intubation: resuscitation with intubation at birth, RDS: respiratory distress syndrome, PPHN: persistent pulmonary hypertension of the newborn, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis,

Appendix

List of institutions and representative physicians enrolled in the database of the Neonatal Research Network Japan

Kushiro Red Cross Hospital: Noro A; Iwate Medical University: Chida S; Sendai Red Cross Hospital: Takahashi R; Fukushima Medical University: Imamura T; Dokkyo Medical University: Suzumura H; Gunma Children's Medical Center: Fujiu T; Saitama Children's Medical Center: Shimizu M; Saitama Medical University Saitama Medical Center: Kunikata T; Tokyo Women's Medical University: Uchiyama A; Aiiku Hospital: Ishii N; Nihon University Itabashi Hospital: Makimoto M; Teikyo University: Hoshi J; Showa University: Aizawa M; Japan Red Cross Medical Center: Kawakami Y; Toho University: Yoda H; Tokyo Metropolitan Bokuto Hospital: Watanabe T; Kanagawa Children's Medical Center: Itani H; Yamanashi Prefectural Central Hospital: Nemoto A; Nagano Children's Hospital: Nakamura T; Nagaoka Red Cross Hospital: Nagata O; Toyama Prefectural Central Hospital; Hutatani T; Seirei Hamamatsu General Hospital; Oki S; Nagoya Red Cross First Hospital: Suzuki C; National Mie Hospital: Bonno M; Kyoto Red Cross First Hospital: Kihara M; Osaka Medical Center and Research Institute for Maternal and Child Health: Shiraishi J; Osaka City General Hospital: Ichiba H; Hyogo Prefectural Kobe Children's Hospital: Yoshimoto S; Nara Medical University: Takahashi Y; Kurashiki Central Hospital: Watabe S; Hiroshima Prefectural Hospital: Fukuhara R; National Kagawa Children's Hospital: Ohta A; Ehime Prefectural Central Hospital: Akiyoshi S; St. Mary's Hospital: Shimokawa S; Kitakyushu City Municipal Medical Center: Matsumoto N; Fukuoka University: Oota E; Kumamoto City Hospital: Kondo Y; Okinawa Chubu Hospital: Kohama M.

Acknowledgement: This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan.

Ethical approve

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

Conflicts of interest

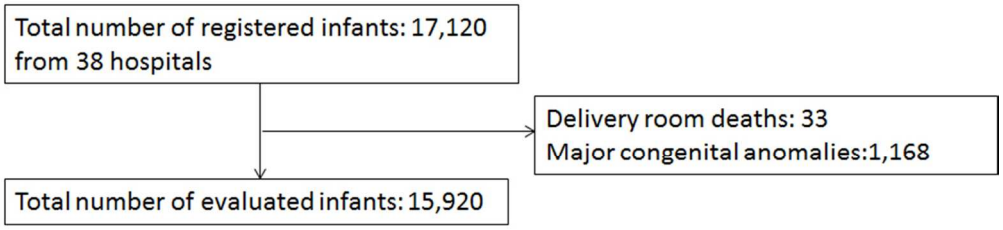
This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan to SK and MF. Thus, the data collection from the participating hospitals was performed by assistants employed under the grand. All information about the infants was collected anonymously, and the data were stored under the responsibility of SK. Other member can access the data after the permission from SK and MF. There was no participation from the funder in the writing and the decision of publication of this manuscript.

Contributorship statement

All authors participated in design of the study. SK, AU, HN, and ST participated in data analysis. MF directed statistical analyses. All co-authors had reviewed the draft of the manuscript and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.



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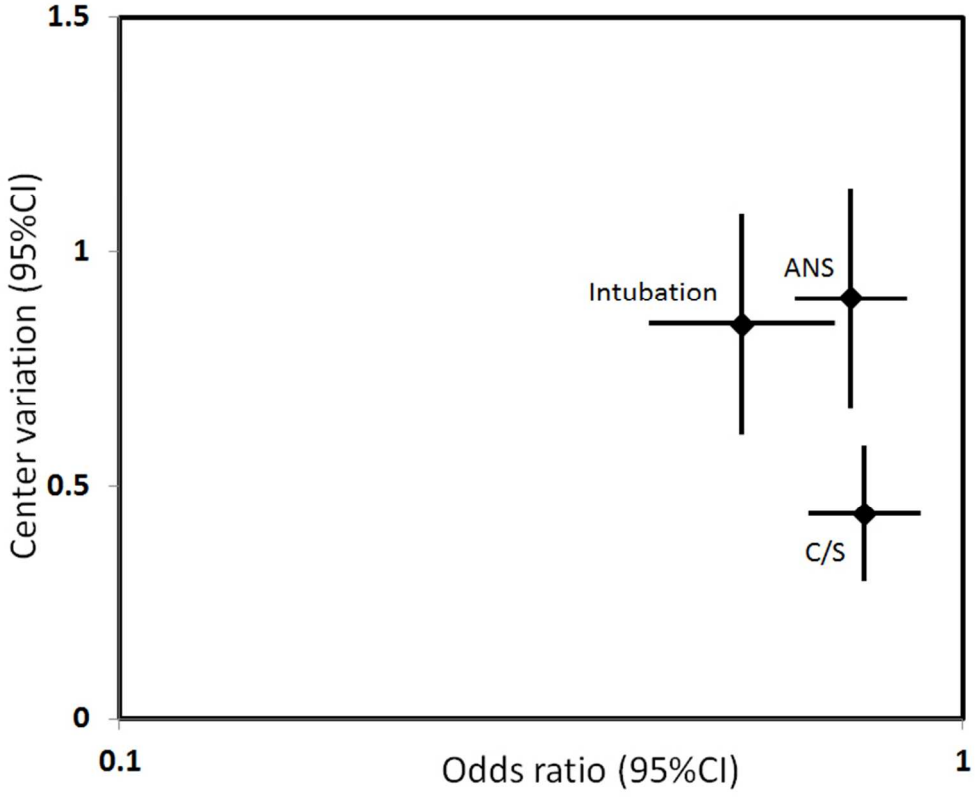

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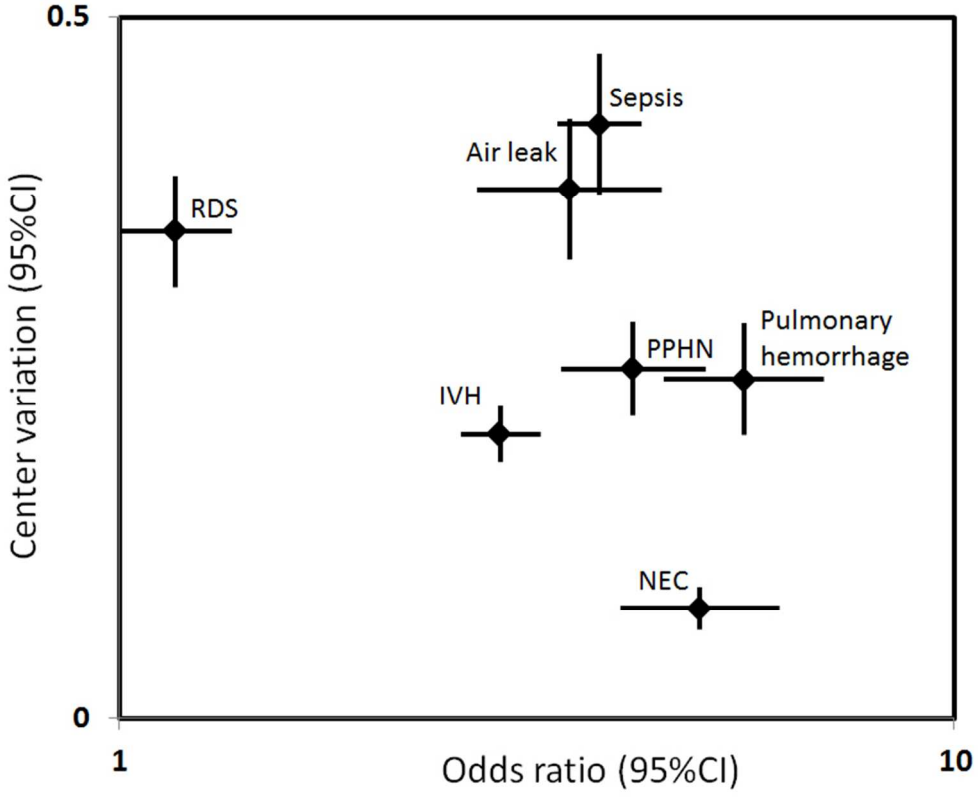

285x237mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Item number and responses

1	(a) Line 7, page 4
	(b) Pages 3 and 5
2	Pages 3 and 5
3	Line 19, page7
4	Line 2, page 8
5	Line 7-11, page 8
6	Line 9, page 8
7	Line 16, page 8
8	Line 16, page 8
9	Line 11, page 8
10	Not applicable
11	Not applicable
12	(a) Line 18, page 8-Line 5, page 9
	(b) Not applicable
	(c) Line 13, page 8
	(d) Not applicable
	(e) Not applicable
13	(a) Figure 1
	(b) Figure 1
	(c) Figure 1
14	(a) Not applicable
	(b) Line 13, page 8
	(c) Line 13, page 8
15	Figure 1
16	(a) Table 1
	(b) Not applicable
	(c) Not applicable
17	Figure 2 and 4
18	Line 2-7, page 12
19	Line 10, page 13
20	Not applicable
21	Line 17, page 13
22	Line 1, page 21

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology
Keywords:	NEONATOLOGY, STATISTICS & RESEARCH METHODS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Running title: practices and morbidities, and outcomes in preterm infants

Abstract

Objectives: In order to determine the feasibility of clinical trials of newly developed treatments or standardization of existing practices to further improve outcomes among very-low-birth-weight (VLBW) infants, a nationwide database was analyzed with a two-dimensional approach using two multivariate logistic models.

Design: Retrospective observational analysis.

Setting: Level III perinatal centers in Japan.

Participants: 15,920 VLBW infants admitted at 38 participating centers from 2003 through 2010.

Outcome measures: Clinical information for the infants was collected until discharge from the centers. A multivariate logistic model identified practices and morbidities associated with mortality. Then, those which were significantly associated with mortality were analyzed using a multilevel logistic model. The residues calculated by the multilevel analysis were used as an indicator of center variation.

Results: Among practices, antenatal steroids and intubation at birth showed relatively high center variations (0.9 and 0.8) and favorable odds ratios (0.7 and 0.5) for mortality, while Cesarean section showed a low center variation (0.4) and a favorable odds ratio (0.8). Sepsis and air leak showed high center variations (0.4 and 0.4) and high odds ratios (3.8 and 3.4) among morbidities. Pulmonary hemorrhage, persistent pulmonary hypertension of the newborn, and intraventricular hemorrhage showed moderate variations (0.2, 0.3, and 0.2, respectively) and high odds ratios (5.6, 4.1, and 2.9, respectively). In contrast, necrotizing enterocolitis showed the lowest variation (0.1) and a high odds ratio (4.9).

Conclusion: The two-dimensional approach has clearly demonstrated the importance of clinical trial or standardization. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques, while standardization must be considered for practices and morbidities with a high center variation.

Trial registration: The database was registered as UMIN000006961.

Article summary

Article Focus:

X: There exists a center variation in practices and incidences of morbidities among high risk infants.

X: If the center variation is wide, the standardization of established treatment is more important than the introduction of a new practice by clinical trial.

X: An analysis of network database may provide the necessity of clinical trial or standardization.

Key messages:

X: Risk-adjusted center variations of interventions and morbidities among high risk infants were calculated using a multilevel analysis.

X: The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques.

X: In contrast, standardization must be considered for practices and morbidities with a high center variation.

Strengths and Limitations:

X: The strength of the study is that all analysis was derived from a large database.

X: The limitation of the study is that limited number of hospitals participated the study.

Key words: standardization, neonate, research network, variation, multilevel analysis

<Introduction>

Although there have been constant advances in neonatal care, there is still significant room to improve outcomes in very-low-birth-weight (VLBW) infants.[1–6] If some interventions or morbidities are strongly associated with outcomes, they should be improved through newly introduced treatments. However, it is also true that there is center variation in interventions and the incidences of morbidities.[7] Routine practices may vary even among level III neonatal intensive care units (NICUs). If this center variation is associated with increased mortality, the standardization of these practices is more pressing than the introduction of a new treatment for the improvement of outcomes of VLBW infants. Because the practices and morbidities in hospitals can be affected by both the relevance of risk and center variation, a two-dimensional approach using two multivariate logistic models was used in this study. The first dimension estimated the risk of an individual practice or morbidity in association with mortality using a linear logistic model by controlling for background risk factors. The second dimension evaluated the center variation in practices and morbidities using a multilevel logistic analysis including individual hospital as an independent variable. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques. In contrast, if the center variation is high, the standardization of established treatments among hospitals through the implementation of guidelines is more important than a newly introduced clinical trial. Thus, we hypothesized that this type of approach of two-dimensional plotting is useful to distinguish between clinical trials and standardization to further improve outcomes among VLBW infants.

<Subjects & Methods>

Study design

The study is an observational analysis of the neonatal database. All data were retrospectively analyzed.

Patient selection

A neonatal research network database in Japan was used in the present study. The database included infants with birth weights at or less than 1,500 g who were treated in participating neonatal centers. To characterize the risk of each practice or morbidity with mortality and their center variation among hospitals, 17,156 infants born from 2003 through 2010 at 38 hospitals that participated in the network throughout the 8 years were analyzed. Among all the infants, 33 infants died in the delivery room, and 1,168 infants with major congenital anomalies were excluded from the study because mortality in those infants was beyond the quality of NICU care. Furthermore, 35 infants were also excluded due to incomplete data registration. Thus, 15,920 infants were included in the study (Fig 1). All 38 hospitals were designated as level III perinatal centers. The definitions of the collected variables were as previously reported, and available on web (http://plaza.umin.ac.jp/nrndata/).[7]

Statistics

1) Identifying risk factors at birth for mortality

To identify risk factors at birth for mortality among VLBW infants, a linear logistic model was introduced using dead in the NICU as a dependent factor. The risk factors tested were

maternal age, primipara, multiple pregnancy, pregnancy-induced hypertension (PIH), diabetes mellitus, clinically diagnosed chorioamnionitis, fetal heart rate abnormalities (NRFS: non-reassuring fetal status), delivery presentation, mode of delivery, gestational age, birth weight, gender, and 1 min Apgar score. Independent variables of mortality were used in this model to adjust background risks of the infants for the following analyses.

2) Calculating odds ratios of practices and morbidities for mortality

To calculate the odds for mortality, another linear logistic regression model was established. In this model, all of the above variables that were independent risk factors for mortality were included. Furthermore, each practice or morbidity was included as an independent variable in the model. To evaluate positive risks for mortality, each practice and morbidity was converted to produce odds ratios more than 1.0, if necessary.

The hospital practices analyzed for association with mortality in the infants were antenatal steroids (ANSs), Cesarean section (C/S), neonatal transport, cord blood transfusion, oxygen use at birth, intubation at birth, continuous positive airway pressure, mechanical ventilation, high-frequency oscillatory ventilation, pulmonary surfactant, inhaled nitric oxide, indomethacin, patent ductus arteriosus (PDA) ligation, glucocorticoid for chronic lung disease (CLD), and intravenous alimentation.

The morbidities analyzed among the infants were respiratory distress syndrome (RDS), air leak syndrome, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn (PPHN), CLD at 28 days after birth, CLD at 36 weeks of corrected age, symptomatic PDA, late-onset adrenal insufficiency of prematurity, intraventricular hemorrhage (IVH), IVH grade

III/IV, periventricular leukomalacia, sepsis, and necrotizing enterocolitis (NEC)/intestinal perforation. All these variables were tested for their independent effect on mortality using a stepwise logistic analysis.

3) Calculating center variations

Another logistic model with multilevel analysis was applied to evaluate hospital variations in each practice and morbidity.[8] In this model, each practice and morbidity was included as a dependent variable. The residues calculated by the multilevel analysis, which indicate the center variations in practice or the incidence of morbidities among the hospitals with an adjustment for background risks of the infants among centers, were used as an indicator of center variations in NICUs for VLBW infants.

4) Statistical methods

All statistical analyses were performed using MLwiN version 2.2 (Center for Multilevel Modeling, University of Bristol, UK).

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

<Results>

1) Risk factors at birth for mortality

The multivariate logistic model showed that multiple pregnancy, PIH, CAM, NRFS, presentation of the fetus, mode of delivery, gestational age more than 37 or less than 24 weeks, birth weight, gender, and Apgar scores <4 at 1 min were considered significant independent variables associated with NICU mortality. These variables were used for adjusting the background risks of the infants for further analyses.

2) Risk-adjusted odds ratios of practices and morbidities and hospital variation

ANSs, C/S, and intubation at birth were practices that were significantly associated with mortality, while RDS, air leak, pulmonary hemorrhage, PPHN, IVH, sepsis, and NEC were morbidities significantly associated with mortality. Center variations were calculated for these practices and morbidities. Table 1 shows the odds ratios and center variations of each practice or morbidity with 95% confidential intervals.

3) Two-dimensional plotting

Figures 2 and 3 show the two-dimensional distribution of odds ratios for mortality and center variations. Among practices, ANSs and intubation at birth showed relatively high center variations and favorable odds ratios for mortality, while C/S showed a low center variation and the same favorable odds ratio. Sepsis and air leak showed high center variations and high odds ratios for mortality among morbidities. Pulmonary hemorrhage, PPHN, and IVH showed moderate variations and high odds ratios. In contrast, NEC showed the lowest variation, with a high odds ratio.

<Discussion>

The two-dimensional approach described here clearly distinguished between the standardization of established treatments and the introduction of new treatment for the further improvement of outcomes among VLBW infants as we hypothesized. If there is a wide center variation in practices or morbidities, standardizing current practices or preventing morbidities must be considered first. In contrast, if the center variation is small, a new intervention for improvement needs to be tested.

ANSs and intubation at birth were among practices that had a less than 1 odds ratio for mortality and a high center variation. For these practices, standardization should be introduced for improvement. Specifically, the benefit of ANSs is already well proved. Thus, the standardization of this practice would not be difficult. Intubation at birth seems to be favorable for saving VLBW infants. However, the beneficial effect on morbidities, such as CLD and retinopathy of prematurity, must be considered from a different point of view. C/S showed an odds ratio less than 1 and low center variation. Thus, a clinical trial to demonstrate the efficacy of C/S when delivering VLBW infants is necessary before it is used as a routine practice.

Among morbidities, sepsis and air leak showed high center variations and high odds ratios for mortality. It would be difficult to introduce a new intervention to reduce these morbidities before standardizing daily practices in NICUs. If some NICUs with these high morbidities can change their routine practices to reduce their incidence, it may be more effective rather than to develop new treatments. IVH, PPHN, and pulmonary hemorrhage had high odds ratios for mortality. However, their center variations were moderate. For these

morbidities, standardization and the development of new treatment will be essential. In contrast, the odds ratio of NEC was high, while its center variation was the smallest among the morbidities. Although the incidence of NEC is very low in Japan, the mortality rate of the infants with NEC is still high. This result indicates that new treatment is necessary to reduce this morbidity.

We have often experienced that the introduction of a newly invented intervention with a high expectancy failed to prove its efficacy in a clinical trial. In this case, wide center variation might compromise the benefit of the intervention. The importance of surveying center variation was previously reported.[9] Furthermore, center variation actually impaired several important clinical trials.[10,11] We believe that our analysis can answer the question of which comes first, clinical trial or standardization.

The limitation of this study is that the analysis was performed only among 38 hospitals, and therefore, the tendency shown in the study does not reflect a nationwide trend. However, these hospitals are leading NICUs, and covering 30% of total VLBW infants born in Japan. Thus, the center variations among these NICUs are hypothesized to be the smallest in Japan. If we included all NICUs in the country, we would have observed wider center variations. We believe that the analysis of a limited number of hospitals is appropriate for this type of study. Additionally, the database does not include information about the timing of morbidities. Thus, a separate time to event analysis on each morbidity is necessary. Furthermore, the direct relationship between interventions and mortality was not evaluated in this study. Thus, the recommendation of C/S and intubation at birth could not be warranted to all VLBW infants.

In conclusion, the simultaneous evaluation of the risks and the center variations in practices or morbidities are useful to find the new strategy for the further improvement of outcomes in VLBW infants. This kind of approach is also reasonable and important in another field of medicine, if there is the probability of center variations in practices and morbidities.

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Figure legend

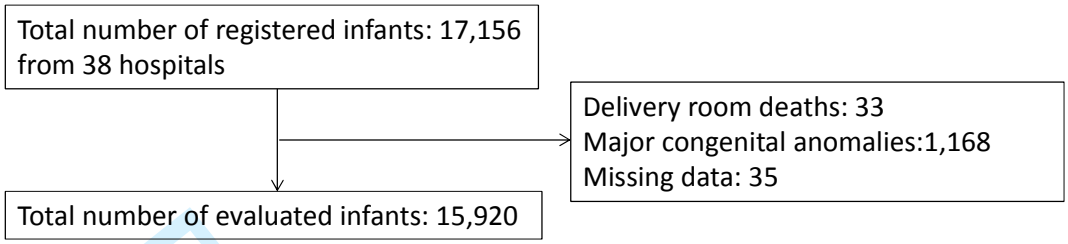

Fig. 1 Flowchart of registration and evaluation

Total 17,156 infants whose birth weight at or less than 1500g were registered on the database. Among them, 33 infants with delivery room death regardless of vigorous resuscitation, 1,168 infants with major congenital anomalies, and 35 infants with incomplete registration were excluded from the study.

Thus, the number of infants evaluated was 15,920, which were reported from 38 hospitals during the study year 2003 through 2010.

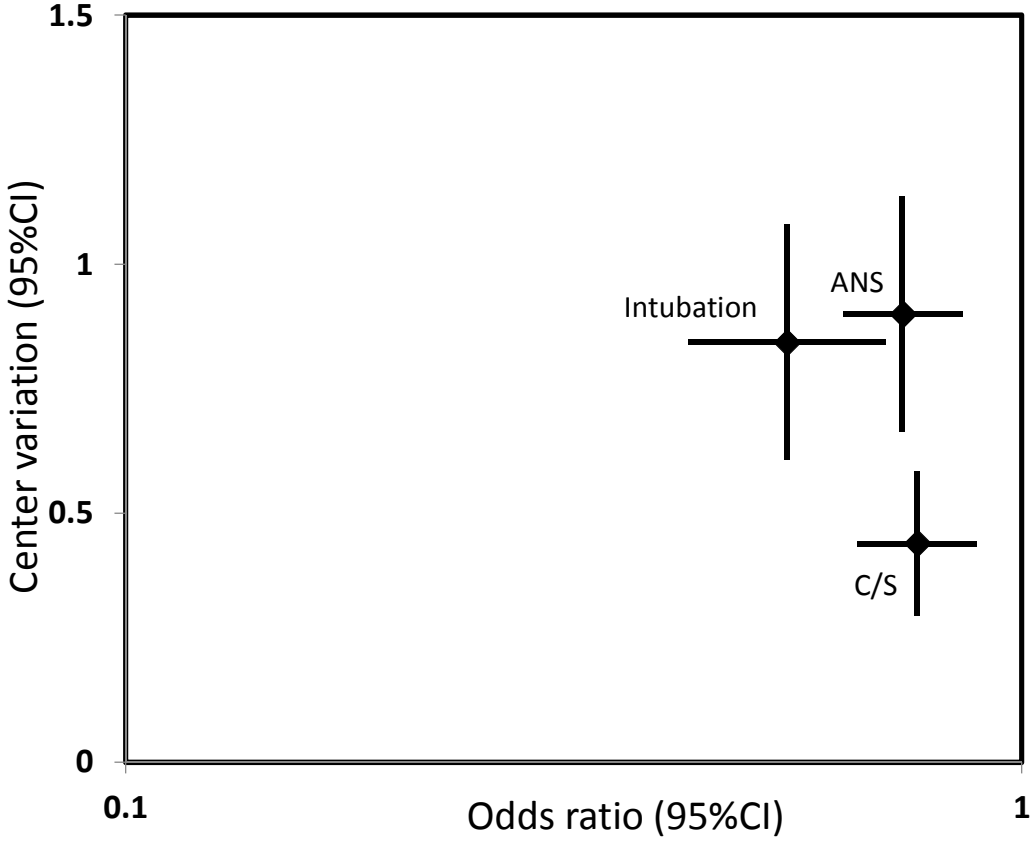

Fig. 2 Distribution of odds ratios for mortality and center variations in practices

The x-axis shows risk-adjusted odds ratios of each practice for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each practice among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

ANSs: antenatal steroids, Intubation: resuscitation with intubation at birth, C/S: Cesarean section

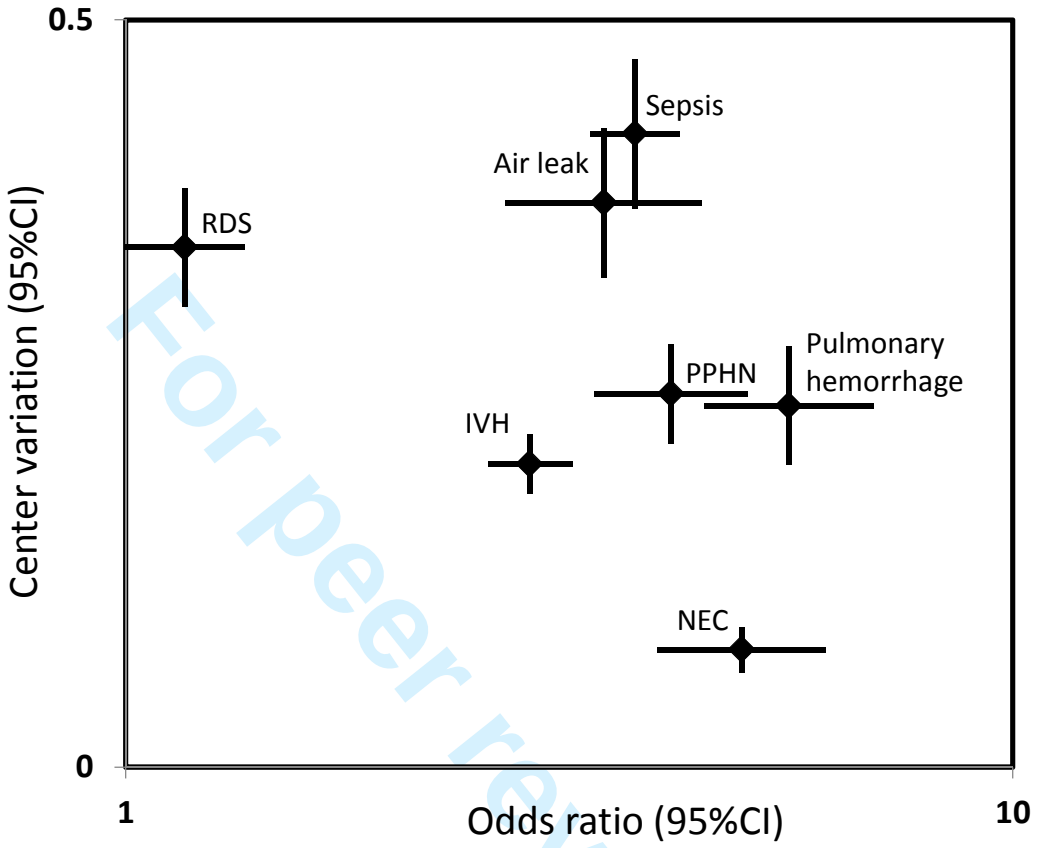

Fig. 3 Distribution of odds ratios for mortality and center variations in morbidities

The x-axis shows risk-adjusted odds ratios of each morbidity for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each morbidity among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome

Table

Table Odds ratios and center variation among practices or morbidities

Practice/Morbidity	Odds ratio (95%CI)		Center variation (95%CI)	
Practice				
ANS	0.7	(0.6–0.9)	0.9	(0.5–1.3)
C/S	0.8	(0.7–0.9)	0.4	(0.2–0.6)
Intubation	0.5	(0.4–0.7)	0.8	(0.5–1.2)
Morbidity				
RDS	1.2	(1.0–1.4)	0.3	(0.2–0.5)
Air leak	3.4	(2.7–4.5)	0.4	(0.2–0.6)
Pulmonary hemorrhage	5.6	(4.4–6.9)	0.2	(0.1–0.4)
PPHN	4.1	(3.4–5.0)	0.3	(0.1–0.4)
IVH	2.9	(2.5–3.3)	0.2	(0.1–0.3)
Sepsis	3.8	(3.2–4.4)	0.4	(0.2–0.6)
NEC	4.9	(3.9–6.2)	0.1	(0.0–0.2)

ANSs: antenatal steroids, C/S: Cesarean section, Intubation: resuscitation with intubation at birth, RDS: respiratory distress syndrome, PPHN: persistent pulmonary hypertension of the newborn, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis,

Appendix

List of institutions and representative physicians enrolled in the database of the Neonatal Research Network Japan

Kushiro Red Cross Hospital: Noro A; Iwate Medical University: Chida S; Sendai Red Cross Hospital: Takahashi R; Fukushima Medical University: Imamura T; Dokkyo Medical University: Suzumura H; Gunma Children's Medical Center: Fujiu T; Saitama Children's Medical Center: Shimizu M; Saitama Medical University Saitama Medical Center: Kunikata T; Tokyo Women's Medical University: Uchiyama A; Aiiku Hospital: Ishii N; Nihon University Itabashi Hospital: Makimoto M; Teikyo University: Hoshi J; Showa University: Aizawa M; Japan Red Cross Medical Center: Kawakami Y; Toho University: Yoda H; Tokyo Metropolitan Bokuto Hospital: Watanabe T; Kanagawa Children's Medical Center: Itani H; Yamanashi Prefectural Central Hospital: Nemoto A; Nagano Children's Hospital: Nakamura T; Nagaoka Red Cross Hospital: Nagata O; Toyama Prefectural Central Hospital; Hutatani T; Seirei Hamamatsu General Hospital; Oki S; Nagoya Red Cross First Hospital: Suzuki C; National Mie Hospital: Bonno M; Kyoto Red Cross First Hospital: Kihara M; Osaka Medical Center and Research Institute for Maternal and Child Health: Shiraishi J; Osaka City General Hospital: Ichiba H; Hyogo Prefectural Kobe Children's Hospital: Yoshimoto S; Nara Medical University: Takahashi Y; Kurashiki Central Hospital: Watabe S; Hiroshima Prefectural Hospital: Fukuhara R; National Kagawa Children's Hospital: Ohta A; Ehime Prefectural Central Hospital: Akiyoshi S; St. Mary's Hospital: Shimokawa S; Kitakyushu City Municipal Medical Center: Matsumoto N; Fukuoka University: Oota E; Kumamoto City Hospital: Kondo Y; Okinawa Chubu Hospital: Kohama M.

Acknowledgement: This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan.

Ethical approve

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

Conflicts of interest

This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan to SK and MF. Thus, the data collection from the participating hospitals was performed by assistants employed under the grand. All information about the infants was collected anonymously, and the data were stored under the responsibility of SK. Other member can access the data after the permission from SK and MF. There was no participation from the funder in the writing and the decision of publication of this manuscript.

Contributorship statement

Satoshi Kusuda (SK), Atushi Uchiyama (AU), Hidehiko Nakanishi (HN), and Satsuki Totsu (ST) participated in data collection. SK, AU, HN, ST and Masanori Fujimura (MF) made the study design and analyzed the data. MF directed statistical analyses. SK mainly worked for interpretation of the results. Thus, all authors participated substantially in the study.

All co-authors had reviewed the draft of the manuscript and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.

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III/IV, periventricular leukomalacia, sepsis, and necrotizing enterocolitis (NEC)/intestinal perforation. All these variables were tested for their independent effect on mortality using a stepwise logistic analysis.

3) Calculating center variations

Another logistic model with multilevel analysis was applied to evaluate hospital variations in each practice and morbidity.[8] In this model, each practice and morbidity was included as a dependent variable. The residues calculated by the multilevel analysis, which indicate the center variations in practice or the incidence of morbidities among the hospitals with an adjustment for background risks of the infants among centers, were used as an indicator of center variations in NICUs for VLBW infants.

4) Statistical methods

All statistical analyses were performed using MLwiN version 2.2 (Center for Multilevel Modeling, University of Bristol, UK).

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

<Results>

1) Risk factors at birth for mortality

The multivariate logistic model showed that multiple pregnancy, PIH, CAM, NRFS, presentation of the fetus, mode of delivery, gestational age more than 37 or less than 24 weeks, birth weight, gender, and Apgar scores <4 at 1 min were considered significant independent variables associated with NICU mortality. These variables were used for adjusting the background risks of the infants for further analyses.

2) Risk-adjusted odds ratios of practices and morbidities and hospital variation

ANSs, C/S, and intubation at birth were practices that were significantly associated with mortality, while RDS, air leak, pulmonary hemorrhage, PPHN, IVH, sepsis, and NEC were morbidities significantly associated with mortality. Center variations were calculated for these practices and morbidities. Table 1 shows the odds ratios and center variations of each practice or morbidity with 95% confidential intervals.

3) Two-dimensional plotting

Figures 2 and 3 show the two-dimensional distribution of odds ratios for mortality and center variations. Among practices, ANSs and intubation at birth showed relatively high center variations and favorable odds ratios for mortality, while C/S showed a low center variation and the same favorable odds ratio. Sepsis and air leak showed high center variations and high odds ratios for mortality among morbidities. Pulmonary hemorrhage, PPHN, and IVH showed moderate variations and high odds ratios. In contrast, NEC showed the lowest variation, with a high odds ratio.

<Discussion>

The two-dimensional approach described here clearly distinguished between the standardization of established treatments and the introduction of new treatment for the further improvement of outcomes among VLBW infants as we hypothesized. If there is a wide center variation in practices or morbidities, standardizing current practices or preventing morbidities must be considered first. In contrast, if the center variation is small, a new intervention for improvement needs to be tested.

ANSs and intubation at birth were among practices that had a less than 1 odds ratio for mortality and a high center variation. For these practices, standardization should be introduced for improvement. Specifically, the benefit of ANSs is already well proved. Thus, the standardization of this practice would not be difficult. Intubation at birth seems to be favorable for saving VLBW infants. However, the beneficial effect on morbidities, such as CLD and retinopathy of prematurity, must be considered from a different point of view. C/S showed an odds ratio less than 1 and low center variation. Thus, a clinical trial to demonstrate the efficacy of C/S when delivering VLBW infants is necessary before it is used as a routine practice.

Among morbidities, sepsis and air leak showed high center variations and high odds ratios for mortality. It would be difficult to introduce a new intervention to reduce these morbidities before standardizing daily practices in NICUs. If some NICUs with these high morbidities can change their routine practices to reduce their incidence, it may be more effective rather than to develop new treatments. IVH, PPHN, and pulmonary hemorrhage had high odds ratios for mortality. However, their center variations were moderate. For these

morbidities, standardization and the development of new treatment will be essential. In contrast, the odds ratio of NEC was high, while its center variation was the smallest among the morbidities. Although the incidence of NEC is very low in Japan, the mortality rate of the infants with NEC is still high. This result indicates that new treatment is necessary to reduce this morbidity.

We have often experienced that the introduction of a newly invented intervention with a high expectancy failed to prove its efficacy in a clinical trial. In this case, wide center variation might compromise the benefit of the intervention. The importance of surveying center variation was previously reported.[9] Furthermore, center variation actually impaired several important clinical trials.[10,11] We believe that our analysis can answer the question of which comes first, clinical trial or standardization.

The limitation of this study is that the analysis was performed only among 38 hospitals, and therefore, the tendency shown in the study does not reflect a nationwide trend. However, these hospitals are leading NICUs, and covering 30% of total VLBW infants born in Japan. Thus, the center variations among these NICUs are hypothesized to be the smallest in Japan. If we included all NICUs in the country, we would have observed wider center variations. We believe that the analysis of a limited number of hospitals is appropriate for this type of study. Additionally, the database does not include information about the timing of morbidities. Thus, a separate time to event analysis on each morbidity is necessary. Furthermore, the direct relationship between interventions and mortality was not evaluated in this study. Thus, the recommendation of C/S and intubation at birth could not be warranted to all VLBW infants.

In conclusion, the simultaneous evaluation of the risks and the center variations in practices or morbidities are useful to find the new strategy for the further improvement of outcomes in VLBW infants. This kind of approach is also reasonable and important in another field of medicine, if there is the probability of center variations in practices and morbidities.

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Figure legend

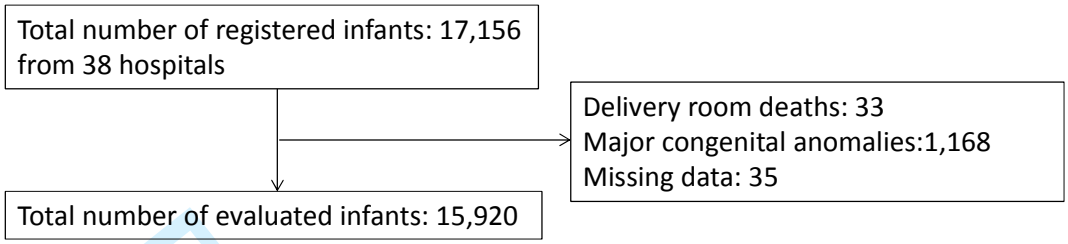


Fig. 1 Flowchart of registration and evaluation

Total 17,156 infants whose birth weight at or less than 1500g were registered on the database. Among them, 33 infants with delivery room death regardless of vigorous resuscitation, 1,168 infants with major congenital anomalies, and 35 infants with incomplete registration were excluded from the study.

Thus, the number of infants evaluated was 15,920, which were reported from 38 hospitals during the study year 2003 through 2010.

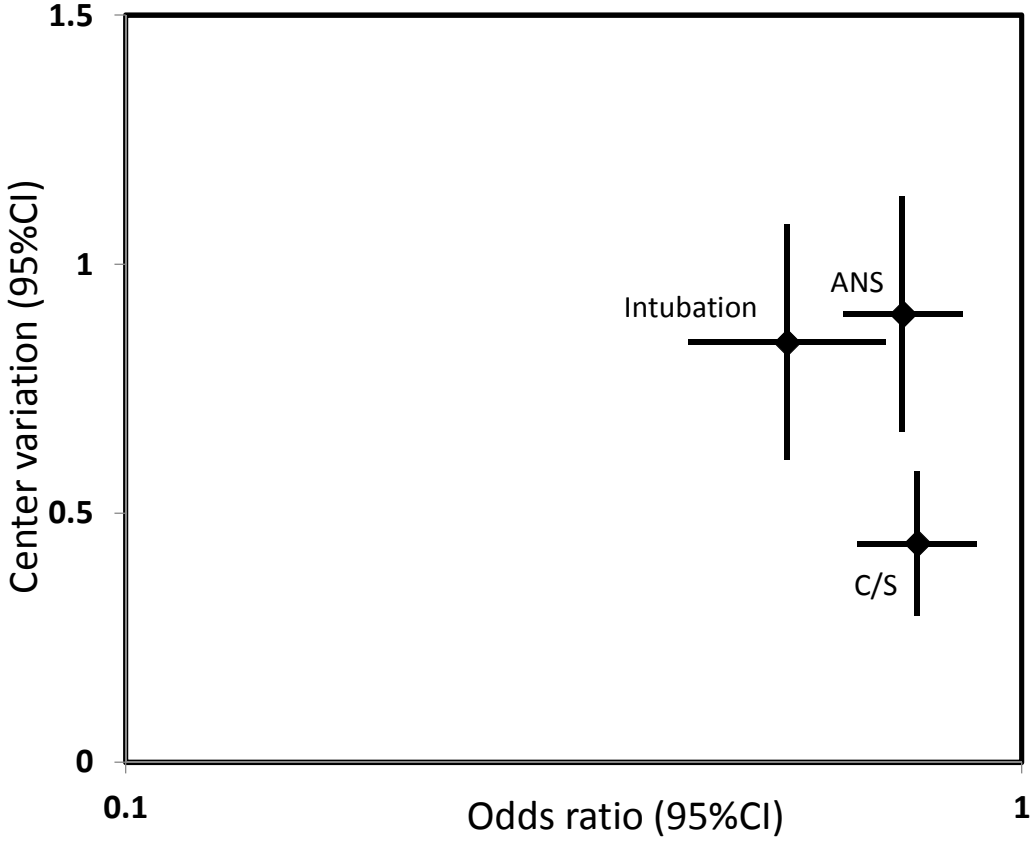


Fig. 2 Distribution of odds ratios for mortality and center variations in practices

The x-axis shows risk-adjusted odds ratios of each practice for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each practice among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

ANSs: antenatal steroids, Intubation: resuscitation with intubation at birth, C/S: Cesarean section

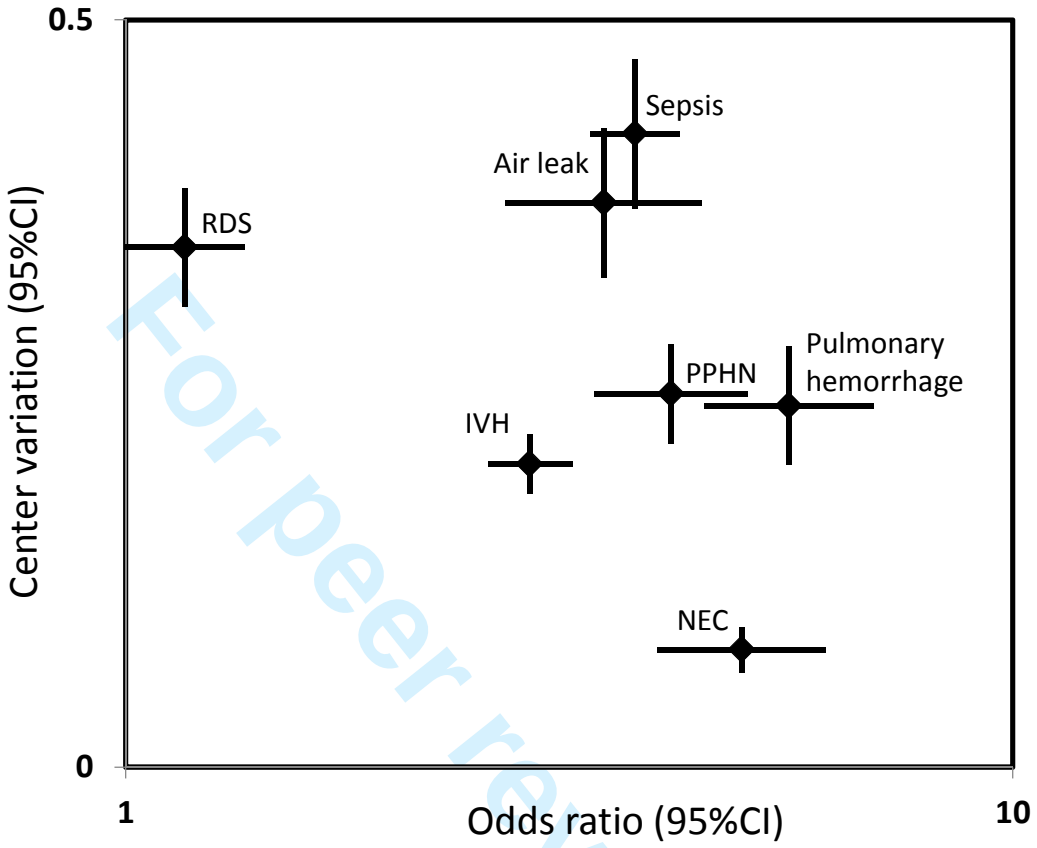


Fig. 3 Distribution of odds ratios for mortality and center variations in morbidities

The x-axis shows risk-adjusted odds ratios of each morbidity for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each morbidity among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome

Table

Table Odds ratios and center variation among practices or morbidities

Practice/Morbidity	Odds ratio (95%CI)		Center variation (95%CI)	
Practice				
ANS	0.7	(0.6–0.9)	0.9	(0.5–1.3)
C/S	0.8	(0.7–0.9)	0.4	(0.2–0.6)
Intubation	0.5	(0.4–0.7)	0.8	(0.5–1.2)
Morbidity				
RDS	1.2	(1.0–1.4)	0.3	(0.2–0.5)
Air leak	3.4	(2.7–4.5)	0.4	(0.2–0.6)
Pulmonary hemorrhage	5.6	(4.4–6.9)	0.2	(0.1–0.4)
PPHN	4.1	(3.4–5.0)	0.3	(0.1–0.4)
IVH	2.9	(2.5–3.3)	0.2	(0.1–0.3)
Sepsis	3.8	(3.2–4.4)	0.4	(0.2–0.6)
NEC	4.9	(3.9–6.2)	0.1	(0.0–0.2)

ANSs: antenatal steroids, C/S: Cesarean section, Intubation: resuscitation with intubation at birth, RDS: respiratory distress syndrome, PPHN: persistent pulmonary hypertension of the newborn, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis,

Appendix

List of institutions and representative physicians enrolled in the database of the Neonatal Research Network Japan

Kushiro Red Cross Hospital: Noro A; Iwate Medical University: Chida S; Sendai Red Cross Hospital: Takahashi R; Fukushima Medical University: Imamura T; Dokkyo Medical University: Suzumura H; Gunma Children's Medical Center: Fujiu T; Saitama Children's Medical Center: Shimizu M; Saitama Medical University Saitama Medical Center: Kunikata T; Tokyo Women's Medical University: Uchiyama A; Aiiku Hospital: Ishii N; Nihon University Itabashi Hospital: Makimoto M; Teikyo University: Hoshi J; Showa University: Aizawa M; Japan Red Cross Medical Center: Kawakami Y; Toho University: Yoda H; Tokyo Metropolitan Bokuto Hospital: Watanabe T; Kanagawa Children's Medical Center: Itani H; Yamanashi Prefectural Central Hospital: Nemoto A; Nagano Children's Hospital: Nakamura T; Nagaoka Red Cross Hospital: Nagata O; Toyama Prefectural Central Hospital; Hutatani T; Seirei Hamamatsu General Hospital; Oki S; Nagoya Red Cross First Hospital: Suzuki C; National Mie Hospital: Bonno M; Kyoto Red Cross First Hospital: Kihara M; Osaka Medical Center and Research Institute for Maternal and Child Health: Shiraishi J; Osaka City General Hospital: Ichiba H; Hyogo Prefectural Kobe Children's Hospital: Yoshimoto S; Nara Medical University: Takahashi Y; Kurashiki Central Hospital: Watabe S; Hiroshima Prefectural Hospital: Fukuhara R; National Kagawa Children's Hospital: Ohta A; Ehime Prefectural Central Hospital: Akiyoshi S; St. Mary's Hospital: Shimokawa S; Kitakyushu City Municipal Medical Center: Matsumoto N; Fukuoka University: Oota E; Kumamoto City Hospital: Kondo Y; Okinawa Chubu Hospital: Kohama M.

Acknowledgement: This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan.

Ethical approve

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

Conflicts of interest

This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan to SK and MF. Thus, the data collection from the participating hospitals was performed by assistants employed under the grand. All information about the infants was collected anonymously, and the data were stored under the responsibility of SK. Other member can access the data after the permission from SK and MF. There was no participation from the funder in the writing and the decision of publication of this manuscript.

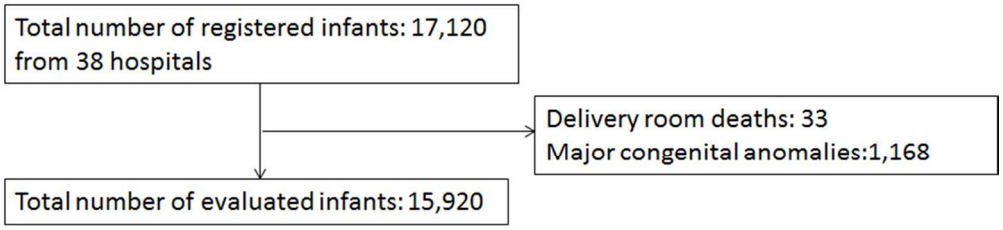
Contributorship statement

Satoshi Kusuda (SK), Atushi Uchiyama (AU), Hidehiko Nakanishi (HN), and Satsuki Totsu (ST) participated in data collection. SK, AU, HN, ST and Masanori Fujimura (MF) made the study design and analyzed the data. MF directed statistical analyses. SK mainly worked for interpretation of the results. Thus, all authors participated substantially in the study.

All co-authors had reviewed the draft of the manuscript and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.



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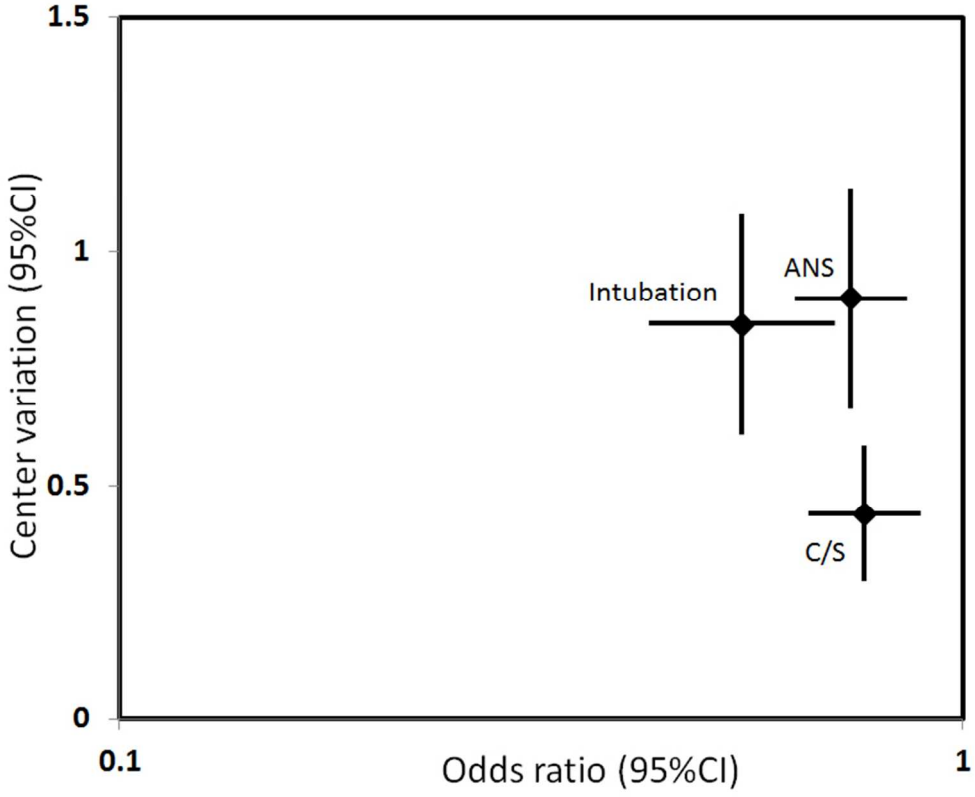

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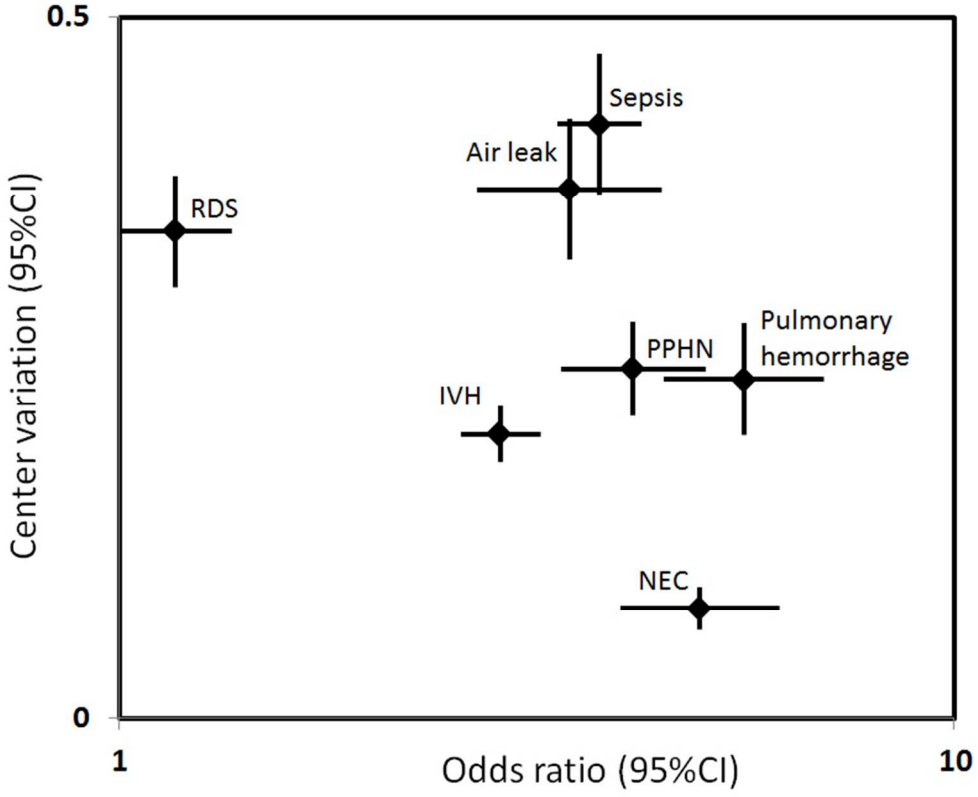

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Item number and responses

1	(a) Line 7, page 4
	(b) Pages 3 and 5
2	Pages 3 and 5
3	Line 19, page7
4	Line 2, page 8
5	Line 7-11, page 8
6	Line 9, page 8
7	Line 16, page 8
8	Line 16, page 8
9	Line 11, page 8
10	Not applicable
11	Not applicable
12	(a) Line 18, page 8-Line 5, page 9
	(b) Not applicable
	(c) Line 13, page 8
	(d) Not applicable
	(e) Not applicable
13	(a) Figure 1
	(b) Figure 1
	(c) Figure 1
14	(a) Not applicable
	(b) Line 13, page 8
	(c) Line 13, page 8
15	Figure 1
16	(a) Table 1
	(b) Not applicable
	(c) Not applicable
17	Figure 2 and 4
18	Line 2-7, page 12
19	Line 10, page 13
20	Not applicable
21	Line 17, page 13
22	Line 1, page 21

Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Running title: practices and morbidities, and outcomes in preterm infants

Abstract

Objectives: In order to determine the feasibility of clinical trials of newly developed treatments or standardization of existing practices to further improve outcomes among very-low-birth-weight (VLBW) infants, a nationwide database was analyzed with a two-dimensional approach using two multivariate logistic models.

Design: Retrospective observational analysis.

Setting: Level III perinatal centers in Japan.

Participants: 15,920 VLBW infants admitted at 38 participating centers from 2003 through 2010.

Outcome measures: Clinical information for the infants was collected until discharge from the centers. A multivariate logistic model identified practices and morbidities associated with mortality. Then, those which were significantly associated with mortality were analyzed using a multilevel logistic model. The residues calculated by the multilevel analysis were used as an indicator of center variation.

Results: Among practices, antenatal steroids and intubation at birth showed relatively high center variations (0.9 and 0.8) and favorable odds ratios (0.7 and 0.5) for mortality, while Cesarean section showed a low center variation (0.4) and a favorable odds ratio (0.8). Sepsis and air leak showed high center variations (0.4 and 0.4) and high odds ratios (3.8 and 3.4) among morbidities. Pulmonary hemorrhage, persistent pulmonary hypertension of the newborn, and intraventricular hemorrhage showed moderate variations (0.2, 0.3, and 0.2, respectively) and

high odds ratios (5.6, 4.1, and 2.9, respectively). In contrast, necrotizing enterocolitis showed the lowest variation (0.1) and a high odds ratio (4.9).

Conclusion: The two-dimensional approach has clearly demonstrated the importance of clinical trial or standardization. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques, while standardization must be considered for practices and morbidities with a high center variation.

Trial registration: The database was registered as UMIN000006961.

Article summary

Article Focus:

X: There exists a center variation in practices and incidences of morbidities among high risk infants.

X: If the center variation is wide, the standardization of established treatment is more important than the introduction of a new practice by clinical trial.

X: An analysis of network database may provide the necessity of clinical trial or standardization.

Key messages:

X: Risk-adjusted center variations of interventions and morbidities among high risk infants were calculated using a multilevel analysis.

X: The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques.

X: In contrast, standardization must be considered for practices and morbidities with a high center variation and high odds ratios for mortality.

Strengths and Limitations:

X: The strength of the study is that all analysis was derived from a large database.

X: The limitation of the study is that limited number of hospitals participated the study.

Key words: standardization, neonate, research network, variation, multilevel analysis

<Introduction>

Although there have been constant advances in neonatal care, there is still significant room to improve outcomes in very-low-birth-weight (VLBW) infants.[1–6] If some interventions or morbidities are strongly associated with poor outcomes, they should be improved through newly introduced treatments. However, it is also true that there is center variation in interventions and the incidences of morbidities.[7] Routine practices may vary even among level III neonatal intensive care units (NICUs). If this center variation is associated with increased mortality, the standardization of these practices is more pressing than the introduction of a new treatment for the improvement of outcomes of VLBW infants. Because the practices and morbidities in hospitals can be affected by both the relevance of risk and center variation, a two-dimensional approach using two multivariate logistic models was used in this study. The first dimension estimated the risk of an individual practice or morbidity in association with mortality using a linear logistic model by controlling for background risk factors. The second dimension evaluated the center variation in practices and morbidities using a multilevel logistic analysis including individual hospital as an independent variable. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques. In contrast, if the center variation is high and the odds ratio of the intervention indicates a decrease in mortality, the standardization of established treatments among hospitals through the implementation of guidelines is more important than a newly introduced clinical trial. Thus, we hypothesized that this type of approach of two-dimensional plotting is useful to distinguish between clinical trials and standardization to further improve outcomes among VLBW infants.

<Subjects & Methods>

Study design

The study is an observational analysis of the neonatal database. All data were retrospectively analyzed.

Patient selection

A neonatal research network database in Japan was used in the present study. The database included infants with birth weights at or less than 1,500 g who were treated in participating neonatal centers. To characterize the risk of each practice or morbidity with mortality and their center variation among hospitals, 17,156 infants born from 2003 through 2010 at 38 hospitals that participated in the network throughout the 8 years were analyzed. Among all the infants, 33 infants died in the delivery room, and 1,168 infants with major congenital anomalies were excluded from the study because mortality in those infants was beyond the quality of NICU care. Furthermore, 35 infants were also excluded due to incomplete data registration. Thus, 15,920 infants were included in the study (Fig 1). All 38 hospitals were designated as level III perinatal centers. The definitions of the collected variables were as previously reported, and available on web (http://plaza.umin.ac.jp/nrndata/).[7]

Statistics

1) Identifying risk factors at birth for mortality

To identify risk factors at birth for mortality among VLBW infants, a linear logistic model was introduced using dead in the NICU as a dependent factor. The risk factors tested were maternal age, primipara, multiple pregnancy, pregnancy-induced hypertension (PIH), diabetes mellitus, clinically diagnosed chorioamnionitis, fetal heart rate abnormalities (NRFS: non-reassuring fetal status), delivery presentation, mode of delivery, gestational age, birth weight, gender, and 1 min Apgar score. Independent variables of mortality were used in this model to adjust background risks of the infants for the following analyses.

2) Calculating odds ratios of practices and morbidities for mortality

To calculate the odds for mortality, another linear logistic regression model was established. In this model, all of the above variables that were independent risk factors for mortality were included. Furthermore, each practice or morbidity was included as an independent variable in the model. To evaluate positive risks for mortality, each practice and morbidity was converted to produce odds ratios more than 1.0, if necessary.

The hospital practices analyzed for association with mortality in the infants were antenatal steroids (ANSs), Cesarean section (C/S), neonatal transport, cord blood transfusion, oxygen use at birth, intubation at birth, continuous positive airway pressure, mechanical ventilation, high-frequency oscillatory ventilation, pulmonary surfactant, inhaled nitric oxide, indomethacin, patent ductus arteriosus (PDA) ligation, glucocorticoid for chronic lung disease (CLD), and intravenous alimentation.

The morbidities analyzed among the infants were respiratory distress syndrome (RDS), air leak syndrome, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn

(PPHN), CLD at 28 days after birth, CLD at 36 weeks of corrected age, symptomatic PDA, late-onset adrenal insufficiency of prematurity, intraventricular hemorrhage (IVH), IVH grade III/IV, periventricular leukomalacia, sepsis, and necrotizing enterocolitis (NEC)/intestinal perforation. All these variables were tested for their independent effect on mortality using a stepwise logistic analysis.

3) Calculating center variations

Another logistic model with a multilevel analysis was applied. [8] The influences of hospital policy towards interventions and patient clustering effects were analyzed using hierarchical structures. The infants were set at the first level variable and the hospitals at the second level, and each practice and morbidity was included as a dependent variable in the multilevel regression model. The residues calculated by the multilevel analysis, which could not be explained with patient clustering, indicate the center variations in practice or the incidence of morbidities among the centers. Unlike a fixed effect model calculated by analysis of variance, the residues estimated by the multilevel analysis are normally-distributed variables with mean zero. Therefore, the mean and standard deviation of residues were used as a useful indicator of center variation. For example a residual value of 0.1 indicates a small center variation, where as a value of 1.0 indicates a relatively large center variation.

4) Statistical methods

All statistical analyses were performed using MLwiN version 2.2 (Center for Multilevel Modeling, University of Bristol, UK).

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

<Results>

1) Risk factors at birth for mortality

The multivariate logistic model showed that multiple pregnancy, PIH, CAM, NRFS, presentation of the fetus, mode of delivery, gestational age more than 37 or less than 24 weeks, birth weight, gender, and Apgar scores <4 at 1 min were considered significant independent variables associated with NICU mortality. These variables were used for adjusting the background risks of the infants for further analyses.

2) Risk-adjusted odds ratios of practices and morbidities and hospital variation

ANSs, C/S, and intubation at birth were practices that were significantly associated with mortality, while RDS, air leak, pulmonary hemorrhage, PPHN, IVH, sepsis, and NEC were morbidities significantly associated with mortality. Center variations were calculated for these practices and morbidities. Table 1 shows the odds ratios and center variations of each practice or morbidity with 95% confidential intervals.

3) Two-dimensional plotting

Figures 2 and 3 show the two-dimensional distribution of odds ratios for mortality and center variations. Among practices, ANSs and intubation at birth showed relatively high center variations and favorable odds ratios for mortality, while C/S showed a low center variation and the same favorable odds ratio. Sepsis and air leak showed high center variations and high odds ratios for mortality among morbidities. Pulmonary hemorrhage, PPHN, and IVH showed moderate variations and high odds ratios. In contrast, NEC showed the lowest variation, with a high odds ratio.

<Discussion>

The two-dimensional approach described here clearly distinguished between the standardization of established treatments and the introduction of new treatment for the further improvement of outcomes among VLBW infants as we hypothesized. If there is a wide center variation in practices or morbidities, standardizing current practices or preventing morbidities must be considered first. In contrast, if the center variation is small, a new intervention for improvement needs to be tested.

ANSs and intubation at birth were among practices that had a less than 1 odds ratio for mortality and a high center variation. For these practices, standardization should be introduced for improvement. Specifically, the benefit of ANSs is already well proved. Thus, the standardization of this practice would not be difficult. Intubation at birth seems to be favorable for saving VLBW infants. However, the beneficial effect on morbidities, such as CLD and retinopathy of prematurity, must be considered from a different point of view. C/S showed an

odds ratio less than 1 and low center variation. Thus, a clinical trial to demonstrate the efficacy of C/S when delivering VLBW infants is necessary before it is used as a routine practice.

Among morbidities, sepsis and air leak showed high center variations and high odds ratios for mortality. It would be difficult to introduce a new intervention to reduce these morbidities before standardizing daily practices in NICUs. If some NICUs with these high morbidities can change their routine practices to reduce their incidence, it may be more effective rather than to develop new treatments. IVH, PPHN, and pulmonary hemorrhage had high odds ratios for mortality. However, their center variations were moderate. For these morbidities, standardization and the development of new treatment will be essential. In contrast, the odds ratio of NEC was high, while its center variation was the smallest among the morbidities. Although the incidence of NEC is very low in Japan, the mortality rate of the infants with NEC is still high. This result indicates that new treatment is necessary to reduce this morbidity.

We have often experienced that the introduction of a newly invented intervention with a high expectancy failed to prove its efficacy in a clinical trial. In this case, wide center variation might compromise the benefit of the intervention. The importance of surveying center variation was previously reported.[9] Furthermore, center variation actually impaired several important clinical trials.[10,11] We believe that our analysis can answer the question of which comes first, clinical trial or standardization.

The limitation of this study is that the analysis was performed only among 38 hospitals, and therefore, the tendency shown in the study does not reflect a nationwide trend. However, these hospitals are leading NICUs, and covering 30% of total VLBW infants born in Japan.

Thus, the center variations among these NICUs are hypothesized to be the smallest in Japan. If we included all NICUs in the country, we would have observed wider center variations. We believe that the analysis of a limited number of hospitals is appropriate for this type of study. Additionally, the database does not include information about the timing of morbidities. Thus, a separate time to event analysis on each morbidity is necessary. Furthermore, the direct relationship between interventions and mortality was not evaluated in this study. Thus, the recommendation of C/S and intubation at birth could not be warranted to all VLBW infants.

In conclusion, the simultaneous evaluation of the risks and the center variations in practices or morbidities are useful to find the new strategy for the further improvement of outcomes in VLBW infants. This kind of approach is also reasonable and important in another field of medicine, if there is the probability of center variations in practices and morbidities.

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Figure legend

Fig. 1 Flowchart of registration and evaluation

Total 17,156 infants whose birth weight at or less than 1500g were registered on the database. Among them, 33 infants with delivery room death regardless of vigorous resuscitation, 1,168 infants with major congenital anomalies, and 35 infants with incomplete registration were excluded from the study.

Thus, the number of infants evaluated was 15,920, which were reported from 38 hospitals during the study year 2003 through 2010.

Fig. 2 Distribution of odds ratios for mortality and center variations in practices

The x-axis shows risk-adjusted odds ratios of each practice for mortality among VLBW infants.

The y-axis shows the risk-adjusted center variation of each practice among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

ANSs: antenatal steroids, Intubation: resuscitation with intubation at birth, C/S: Cesarean section

Fig. 3 Distribution of odds ratios for mortality and center variations in morbidities

The x-axis shows risk-adjusted odds ratios of each morbidity for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each morbidity among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome

Table

Table Odds ratios and center variation among practices or morbidities

Practice/Morbidity	Odds ratio (95%CI)		Center variation (95%CI)	
Practice				
ANS	0.7	(0.6–0.9)	0.9	(0.5–1.3)
C/S	0.8	(0.7–0.9)	0.4	(0.2–0.6)
Intubation	0.5	(0.4–0.7)	0.8	(0.5–1.2)
Morbidity				
RDS	1.2	(1.0–1.4)	0.3	(0.2–0.5)
Air leak	3.4	(2.7–4.5)	0.4	(0.2–0.6)
Pulmonary hemorrhage	5.6	(4.4–6.9)	0.2	(0.1–0.4)
PPHN	4.1	(3.4–5.0)	0.3	(0.1–0.4)
IVH	2.9	(2.5–3.3)	0.2	(0.1–0.3)
Sepsis	3.8	(3.2–4.4)	0.4	(0.2–0.6)
NEC	4.9	(3.9–6.2)	0.1	(0.0–0.2)

ANSs: antenatal steroids, C/S: Cesarean section, Intubation: resuscitation with intubation at birth, RDS: respiratory distress syndrome, PPHN: persistent pulmonary hypertension of the newborn, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis,

Appendix

List of institutions and representative physicians enrolled in the database of the Neonatal Research Network Japan

Kushiro Red Cross Hospital: Noro A; Iwate Medical University: Chida S; Sendai Red Cross Hospital: Takahashi R; Fukushima Medical University: Imamura T; Dokkyo Medical University: Suzumura H; Gunma Children's Medical Center: Fujiu T; Saitama Children's Medical Center: Shimizu M; Saitama Medical University Saitama Medical Center: Kunikata T; Tokyo Women's Medical University: Uchiyama A; Aiiku Hospital: Ishii N; Nihon University Itabashi Hospital: Makimoto M; Teikyo University: Hoshi J; Showa University: Aizawa M; Japan Red Cross Medical Center: Kawakami Y; Toho University: Yoda H; Tokyo Metropolitan Bokuto Hospital: Watanabe T; Kanagawa Children's Medical Center: Itani H; Yamanashi Prefectural Central Hospital: Nemoto A; Nagano Children's Hospital: Nakamura T; Nagaoka Red Cross Hospital: Nagata O; Toyama Prefectural Central Hospital; Hutatani T; Seirei Hamamatsu General Hospital; Oki S; Nagoya Red Cross First Hospital: Suzuki C; National Mie Hospital: Bonno M; Kyoto Red Cross First Hospital: Kihara M; Osaka Medical Center and Research Institute for Maternal and Child Health: Shiraishi J; Osaka City General Hospital: Ichiba H; Hyogo Prefectural Kobe Children's Hospital: Yoshimoto S; Nara Medical University: Takahashi Y; Kurashiki Central Hospital: Watabe S; Hiroshima Prefectural Hospital: Fukuhara R; National Kagawa Children's Hospital: Ohta A; Ehime Prefectural Central Hospital: Akiyoshi S; St. Mary's Hospital: Shimokawa S; Kitakyushu City Municipal Medical Center: Matsumoto N; Fukuoka University: Oota E; Kumamoto City Hospital: Kondo Y; Okinawa Chubu Hospital: Kohama M.

Acknowledgement: This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan.

Ethical approve

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

Conflicts of interest

This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan to SK and MF. Thus, the data collection from the participating hospitals was performed by assistants employed under the grand. All information about the infants was collected anonymously, and the data were stored under the responsibility of SK. Other member can access the data after the permission from SK and MF. There was no participation from the funder in the writing and the decision of publication of this manuscript.

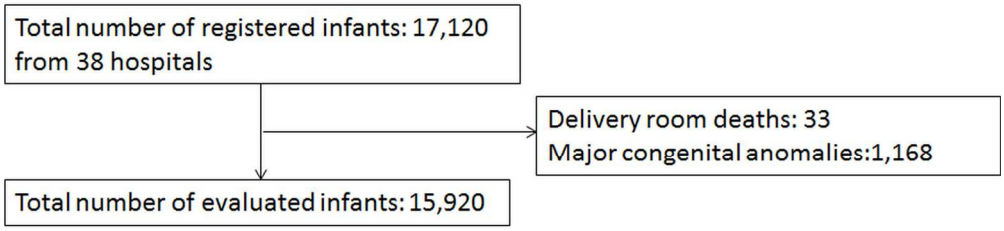
Contributorship statement

Satoshi Kusuda (SK), Atushi Uchiyama (AU), Hidehiko Nakanishi (HN), and Satsuki Totsu (ST) participated in data collection. SK, AU, HN, ST and Masanori Fujimura (MF) made the study design and analyzed the data. MF directed statistical analyses. SK mainly worked for interpretation of the results. Thus, all authors participated substantially in the study.

All co-authors had reviewed the draft of the manuscript and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.



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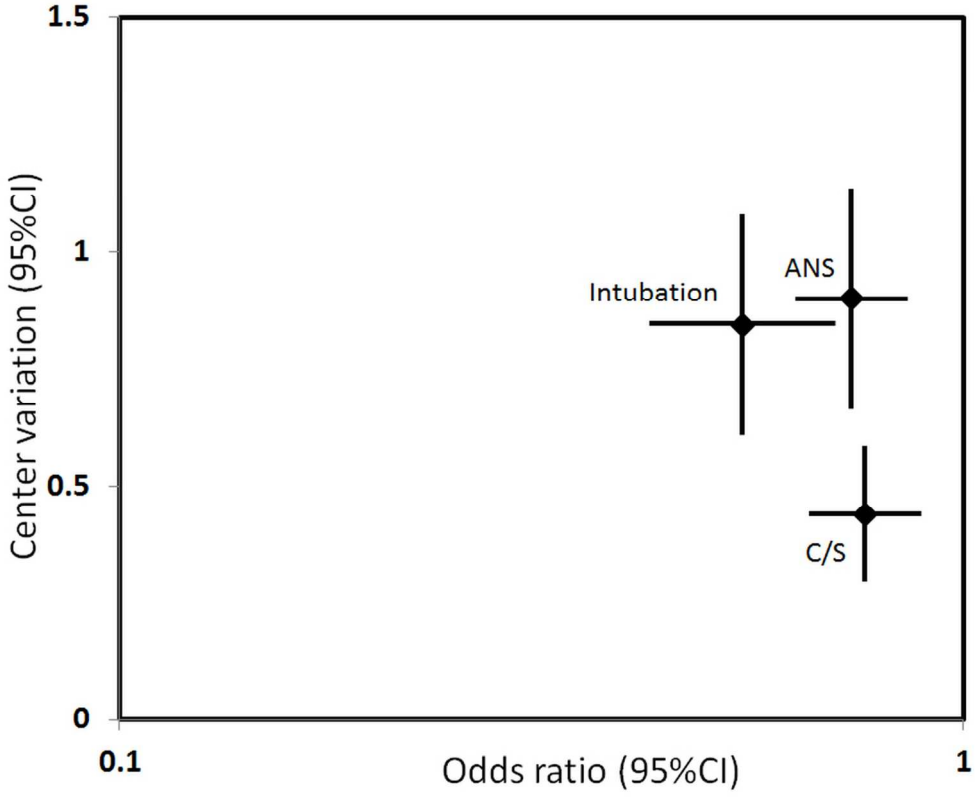

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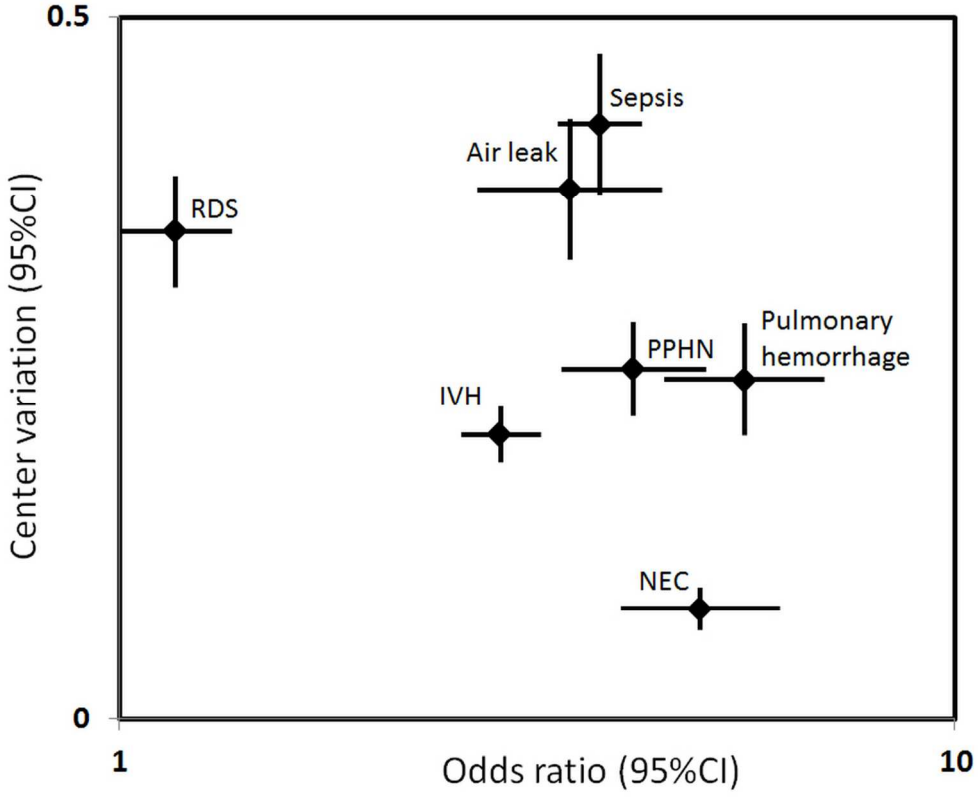

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Item number and responses

1	(a) Line 7, page 4
	(b) Pages 3 and 5
2	Pages 3 and 5
3	Line 19, page7
4	Line 2, page 8
5	Line 7-11, page 8
6	Line 9, page 8
7	Line 16, page 8
8	Line 16, page 8
9	Line 11, page 8
10	Not applicable
11	Not applicable
12	(a) Line 18, page 8-Line 5, page 9
	(b) Not applicable
	(c) Line 13, page 8
	(d) Not applicable
	(e) Not applicable
13	(a) Figure 1
	(b) Figure 1
	(c) Figure 1
14	(a) Not applicable
	(b) Line 13, page 8
	(c) Line 13, page 8
15	Figure 1
16	(a) Table 1
	(b) Not applicable
	(c) Not applicable
17	Figure 2 and 4
18	Line 2-7, page 12
19	Line 10, page 13
20	Not applicable
21	Line 17, page 13
22	Line 1, page 21

Identification of practices and morbidities affecting the mortality of very-low-birth-weight infants using a multilevel logistic analysis: clinical trial or standardization?

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Running title: practices and morbidities, and outcomes in preterm infants

Abstract

Objectives: In order to determine the feasibility of clinical trials of newly developed treatments or standardization of existing practices to further improve outcomes among very-low-birth-weight (VLBW) infants, a nationwide database was analyzed with a two-dimensional approach using two multivariate logistic models.

Design: Retrospective observational analysis.

Setting: Level III perinatal centers in Japan.

Participants: 15,920 VLBW infants admitted at 38 participating centers from 2003 through 2010.

Outcome measures: Clinical information for the infants was collected until discharge from the centers. A multivariate logistic model identified practices and morbidities associated with mortality. Then, those which were significantly associated with mortality were analyzed using a multilevel logistic model. The residues calculated by the multilevel analysis were used as an indicator of center variation.

Results: Among practices, antenatal steroids and intubation at birth showed relatively high center variations (0.9 and 0.8) and favorable odds ratios (0.7 and 0.5) for mortality, while Cesarean section showed a low center variation (0.4) and a favorable odds ratio (0.8). Sepsis and air leak showed high center variations (0.4 and 0.4) and high odds ratios (3.8 and 3.4) among morbidities. Pulmonary hemorrhage, persistent pulmonary hypertension of the newborn, and intraventricular hemorrhage showed moderate variations (0.2, 0.3, and 0.2, respectively) and high odds ratios (5.6, 4.1, and 2.9, respectively). In contrast, necrotizing enterocolitis showed the lowest variation (0.1) and a high odds ratio (4.9).

Conclusion: The two-dimensional approach has clearly demonstrated the importance of clinical trial or standardization. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques, while standardization must be considered for practices and morbidities with a high center variation.

Trial registration: The database was registered as UMIN000006961.

Article summary

Article Focus:

X: There exists a center variation in practices and incidences of morbidities among high risk infants.

X: If the center variation is wide, the standardization of established treatment is more important than the introduction of a new practice by clinical trial.

X: An analysis of network database may provide the necessity of clinical trial or standardization.

Key messages:

X: Risk-adjusted center variations of interventions and morbidities among high risk infants were calculated using a multilevel analysis.

X: The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques.

X: In contrast, standardization must be considered for practices and morbidities with a high center variation and high odds ratios for mortality.

Strengths and Limitations:

X: The strength of the study is that all analysis was derived from a large database.

X: The limitation of the study is that limited number of hospitals participated the study.

Key words: standardization, neonate, research network, variation, multilevel analysis

<Introduction>

Although there have been constant advances in neonatal care, there is still significant room to improve outcomes in very-low-birth-weight (VLBW) infants.[1–6] If some interventions or morbidities are strongly associated with poor outcomes, they should be improved through newly introduced treatments. However, it is also true that there is center variation in interventions and the incidences of morbidities.[7] Routine practices may vary even among level III neonatal intensive care units (NICUs). If this center variation is associated with increased mortality, the standardization of these practices is more pressing than the introduction of a new treatment for the improvement of outcomes of VLBW infants. Because the practices and morbidities in hospitals can be affected by both the relevance of risk and center variation, a two-dimensional approach using two multivariate logistic models was used in this study. The first dimension estimated the risk of an individual practice or morbidity in association with mortality using a linear logistic model by controlling for background risk factors. The second dimension evaluated the center variation in practices and morbidities using a multilevel logistic analysis including individual hospital as an independent variable. The practices and morbidities with low center variations and high odds ratios for mortality must be improved through clinical trials of newly introduced techniques. In contrast, if the center variation is high and the odds ratio of the intervention indicates a decrease in mortality, the standardization of established treatments among hospitals through the implementation of guidelines is more important than a newly introduced clinical trial. Thus, we hypothesized that this type of approach of two-dimensional plotting is useful to distinguish between clinical trials and standardization to further improve outcomes among VLBW infants.

<Subjects & Methods>

Study design

The study is an observational analysis of the neonatal database. All data were retrospectively analyzed.

Patient selection

A neonatal research network database in Japan was used in the present study. The database included infants with birth weights at or less than 1,500 g who were treated in participating neonatal centers. To characterize the risk of each practice or morbidity with mortality and their center variation among hospitals, 17,156 infants born from 2003 through 2010 at 38 hospitals that participated in the network throughout the 8 years were analyzed. Among all the infants, 33 infants died in the delivery room, and 1,168 infants with major congenital anomalies were excluded from the study because mortality in those infants was beyond the quality of NICU care. Furthermore, 35 infants were also excluded due to incomplete data registration. Thus, 15,920 infants were included in the study (Fig 1). All 38 hospitals were designated as level III perinatal centers. The definitions of the collected variables were as previously reported, and available on web (http://plaza.umin.ac.jp/nrndata/).[7]

Statistics

1) Identifying risk factors at birth for mortality

To identify risk factors at birth for mortality among VLBW infants, a linear logistic model was introduced using dead in the NICU as a dependent factor. The risk factors tested were maternal age, primipara, multiple pregnancy, pregnancy-induced hypertension (PIH), diabetes mellitus, clinically diagnosed chorioamnionitis, fetal heart rate abnormalities (NRFS: non-reassuring fetal status), delivery presentation, mode of delivery, gestational age, birth weight, gender, and 1 min Apgar score. Independent variables of mortality were used in this model to adjust background risks of the infants for the following analyses.

2) Calculating odds ratios of practices and morbidities for mortality

To calculate the odds for mortality, another linear logistic regression model was established. In this model, all of the above variables that were independent risk factors for mortality were included. Furthermore, each practice or morbidity was included as an independent variable in the model. To evaluate positive risks for mortality, each practice and morbidity was converted to produce odds ratios more than 1.0, if necessary.

The hospital practices analyzed for association with mortality in the infants were antenatal steroids (ANSs), Cesarean section (C/S), neonatal transport, cord blood transfusion, oxygen use at birth, intubation at birth, continuous positive airway pressure, mechanical ventilation, high-frequency oscillatory ventilation, pulmonary surfactant, inhaled nitric oxide, indomethacin, patent ductus arteriosus (PDA) ligation, glucocorticoid for chronic lung disease (CLD), and intravenous alimentation.

The morbidities analyzed among the infants were respiratory distress syndrome (RDS), air leak syndrome, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn

(PPHN), CLD at 28 days after birth, CLD at 36 weeks of corrected age, symptomatic PDA, late-onset adrenal insufficiency of prematurity, intraventricular hemorrhage (IVH), IVH grade III/IV, periventricular leukomalacia, sepsis, and necrotizing enterocolitis (NEC)/intestinal perforation. All these variables were tested for their independent effect on mortality using a stepwise logistic analysis.

3) Calculating center variations

Another logistic model with a multilevel analysis was applied. [8] The influences of hospital policy towards interventions and patient clustering effects were analyzed using hierarchical structures. The infants were set at the first level variable and the hospitals at the second level, and each practice and morbidity was included as a dependent variable in the multilevel regression model. The residues calculated by the multilevel analysis, which could not be explained with patient clustering, indicate the center variations in practice or the incidence of morbidities among the centers. Unlike a fixed effect model calculated by analysis of variance, the residues estimated by the multilevel analysis are normally-distributed variables with mean zero. Therefore, the mean and standard deviation of residues were used as a useful indicator of center variation. For example a residual value of 0.1 indicates a small center variation, where as a value of 1.0 indicates a relatively large center variation.

4) Statistical methods

All statistical analyses were performed using MLwiN version 2.2 (Center for Multilevel Modeling, University of Bristol, UK).

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

<Results>

1) Risk factors at birth for mortality

The multivariate logistic model showed that multiple pregnancy, PIH, CAM, NRFS, presentation of the fetus, mode of delivery, gestational age more than 37 or less than 24 weeks, birth weight, gender, and Apgar scores <4 at 1 min were considered significant independent variables associated with NICU mortality. These variables were used for adjusting the background risks of the infants for further analyses.

2) Risk-adjusted odds ratios of practices and morbidities and hospital variation

ANSs, C/S, and intubation at birth were practices that were significantly associated with mortality, while RDS, air leak, pulmonary hemorrhage, PPHN, IVH, sepsis, and NEC were morbidities significantly associated with mortality. Center variations were calculated for these practices and morbidities. Table 1 shows the odds ratios and center variations of each practice or morbidity with 95% confidential intervals.

3) Two-dimensional plotting

Figures 2 and 3 show the two-dimensional distribution of odds ratios for mortality and center variations. Among practices, ANSs and intubation at birth showed relatively high center variations and favorable odds ratios for mortality, while C/S showed a low center variation and the same favorable odds ratio. Sepsis and air leak showed high center variations and high odds ratios for mortality among morbidities. Pulmonary hemorrhage, PPHN, and IVH showed moderate variations and high odds ratios. In contrast, NEC showed the lowest variation, with a high odds ratio.

<Discussion>

The two-dimensional approach described here clearly distinguished between the standardization of established treatments and the introduction of new treatment for the further improvement of outcomes among VLBW infants as we hypothesized. If there is a wide center variation in practices or morbidities, standardizing current practices or preventing morbidities must be considered first. In contrast, if the center variation is small, a new intervention for improvement needs to be tested.

ANSs and intubation at birth were among practices that had a less than 1 odds ratio for mortality and a high center variation. For these practices, standardization should be introduced for improvement. Specifically, the benefit of ANSs is already well proved. Thus, the standardization of this practice would not be difficult. Intubation at birth seems to be favorable for saving VLBW infants. However, the beneficial effect on morbidities, such as CLD and retinopathy of prematurity, must be considered from a different point of view. C/S showed an

odds ratio less than 1 and low center variation. Thus, a clinical trial to demonstrate the efficacy of C/S when delivering VLBW infants is necessary before it is used as a routine practice.

Among morbidities, sepsis and air leak showed high center variations and high odds ratios for mortality. It would be difficult to introduce a new intervention to reduce these morbidities before standardizing daily practices in NICUs. If some NICUs with these high morbidities can change their routine practices to reduce their incidence, it may be more effective rather than to develop new treatments. IVH, PPHN, and pulmonary hemorrhage had high odds ratios for mortality. However, their center variations were moderate. For these morbidities, standardization and the development of new treatment will be essential. In contrast, the odds ratio of NEC was high, while its center variation was the smallest among the morbidities. Although the incidence of NEC is very low in Japan, the mortality rate of the infants with NEC is still high. This result indicates that new treatment is necessary to reduce this morbidity.

We have often experienced that the introduction of a newly invented intervention with a high expectancy failed to prove its efficacy in a clinical trial. In this case, wide center variation might compromise the benefit of the intervention. The importance of surveying center variation was previously reported.[9] Furthermore, center variation actually impaired several important clinical trials.[10,11] We believe that our analysis can answer the question of which comes first, clinical trial or standardization.

The limitation of this study is that the analysis was performed only among 38 hospitals, and therefore, the tendency shown in the study does not reflect a nationwide trend. However, these hospitals are leading NICUs, and covering 30% of total VLBW infants born in Japan.

Thus, the center variations among these NICUs are hypothesized to be the smallest in Japan. If we included all NICUs in the country, we would have observed wider center variations. We believe that the analysis of a limited number of hospitals is appropriate for this type of study. Additionally, the database does not include information about the timing of morbidities. Thus, a separate time to event analysis on each morbidity is necessary. Furthermore, the direct relationship between interventions and mortality was not evaluated in this study. Thus, the recommendation of C/S and intubation at birth could not be warranted to all VLBW infants.

In conclusion, the simultaneous evaluation of the risks and the center variations in practices or morbidities are useful to find the new strategy for the further improvement of outcomes in VLBW infants. This kind of approach is also reasonable and important in another field of medicine, if there is the probability of center variations in practices and morbidities.

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Figure legend

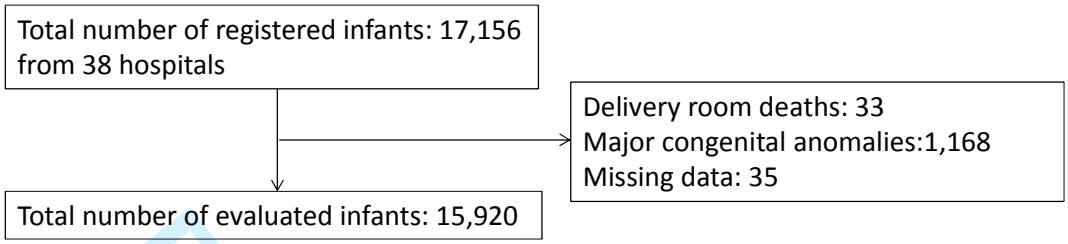

Fig. 1 Flowchart of registration and evaluation

Total 17,156 infants whose birth weight at or less than 1500g were registered on the database. Among them, 33 infants with delivery room death regardless of vigorous resuscitation, 1,168 infants with major congenital anomalies, and 35 infants with incomplete registration were excluded from the study.

Thus, the number of infants evaluated was 15,920, which were reported from 38 hospitals during the study year 2003 through 2010.

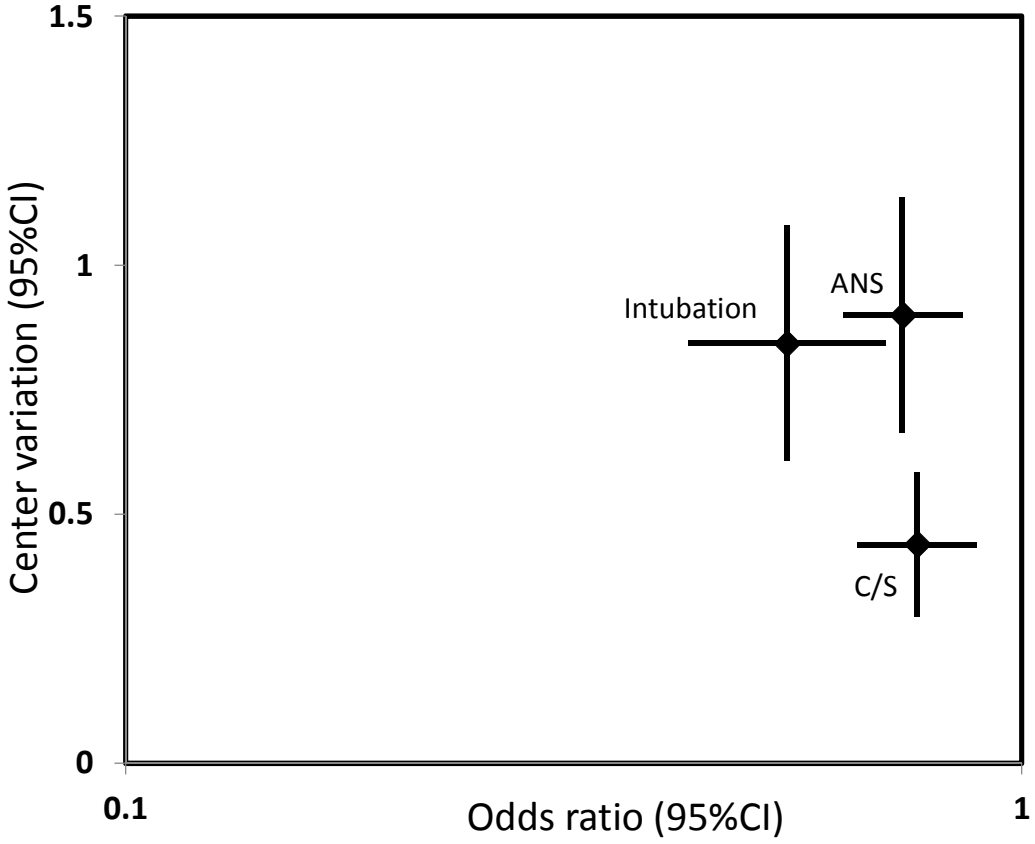

Fig. 2 Distribution of odds ratios for mortality and center variations in practices

The x-axis shows risk-adjusted odds ratios of each practice for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each practice among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

ANSs: antenatal steroids, Intubation: resuscitation with intubation at birth, C/S: Cesarean section

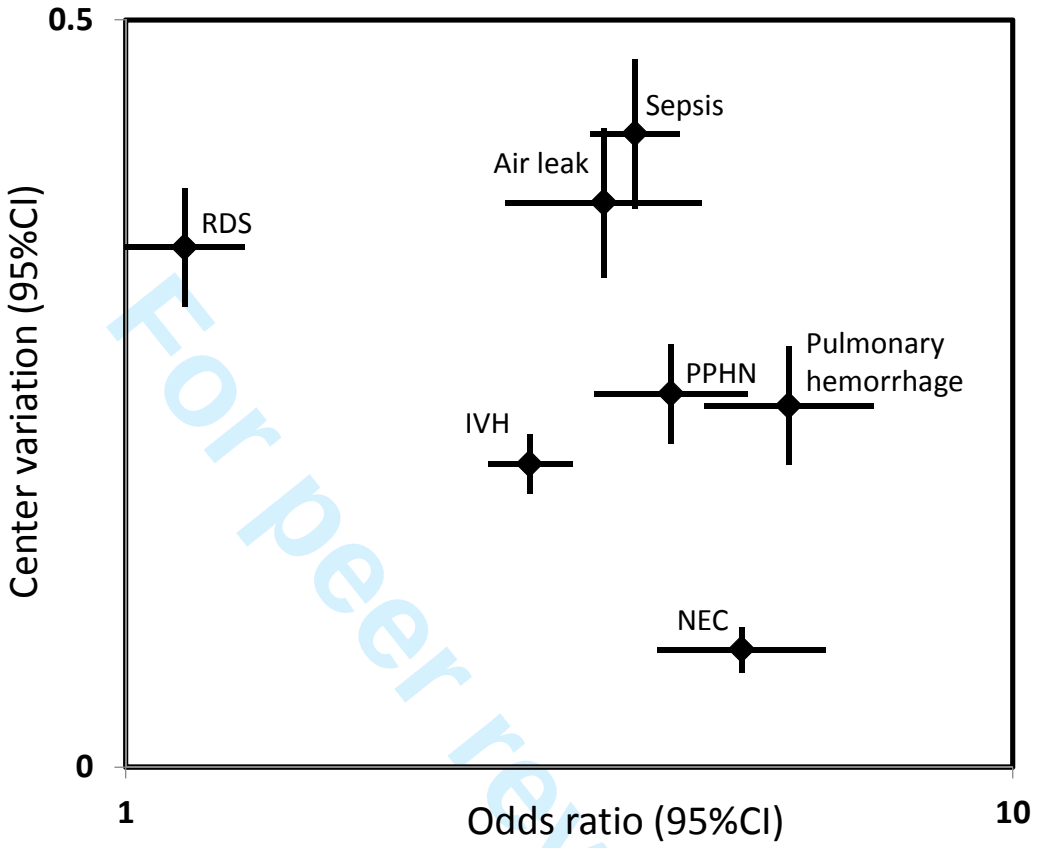

Fig. 3 Distribution of odds ratios for mortality and center variations in morbidities

The x-axis shows risk-adjusted odds ratios of each morbidity for mortality among VLBW infants. The y-axis shows the risk-adjusted center variation of each morbidity among 38 NICUs. Vertical and horizontal bars represent 95% confidential intervals.

IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome

Table

Table Odds ratios and center variation among practices or morbidities

Practice/Morbidity	Odds ratio (95%CI)		Center variation (95%CI)	
Practice				
ANS	0.7	(0.6–0.9)	0.9	(0.5–1.3)
C/S	0.8	(0.7–0.9)	0.4	(0.2–0.6)
Intubation	0.5	(0.4–0.7)	0.8	(0.5–1.2)
Morbidity				
RDS	1.2	(1.0–1.4)	0.3	(0.2–0.5)
Air leak	3.4	(2.7–4.5)	0.4	(0.2–0.6)
Pulmonary hemorrhage	5.6	(4.4–6.9)	0.2	(0.1–0.4)
PPHN	4.1	(3.4–5.0)	0.3	(0.1–0.4)
IVH	2.9	(2.5–3.3)	0.2	(0.1–0.3)
Sepsis	3.8	(3.2–4.4)	0.4	(0.2–0.6)
NEC	4.9	(3.9–6.2)	0.1	(0.0–0.2)

ANSs: antenatal steroids, C/S: Cesarean section, Intubation: resuscitation with intubation at birth, RDS: respiratory distress syndrome, PPHN: persistent pulmonary hypertension of the newborn, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis,

Appendix

List of institutions and representative physicians enrolled in the database of the Neonatal Research Network Japan

Kushiro Red Cross Hospital: Noro A; Iwate Medical University: Chida S; Sendai Red Cross Hospital: Takahashi R; Fukushima Medical University: Imamura T; Dokkyo Medical University: Suzumura H; Gunma Children's Medical Center: Fujiu T; Saitama Children's Medical Center: Shimizu M; Saitama Medical University Saitama Medical Center: Kunikata T; Tokyo Women's Medical University: Uchiyama A; Aiiku Hospital: Ishii N; Nihon University Itabashi Hospital: Makimoto M; Teikyo University: Hoshi J; Showa University: Aizawa M; Japan Red Cross Medical Center: Kawakami Y; Toho University: Yoda H; Tokyo Metropolitan Bokuto Hospital: Watanabe T; Kanagawa Children's Medical Center: Itani H; Yamanashi Prefectural Central Hospital: Nemoto A; Nagano Children's Hospital: Nakamura T; Nagaoka Red Cross Hospital: Nagata O; Toyama Prefectural Central Hospital; Hutatani T; Seirei Hamamatsu General Hospital; Oki S; Nagoya Red Cross First Hospital: Suzuki C; National Mie Hospital: Bonno M; Kyoto Red Cross First Hospital: Kihara M; Osaka Medical Center and Research Institute for Maternal and Child Health: Shiraishi J; Osaka City General Hospital: Ichiba H; Hyogo Prefectural Kobe Children's Hospital: Yoshimoto S; Nara Medical University: Takahashi Y; Kurashiki Central Hospital: Watabe S; Hiroshima Prefectural Hospital: Fukuhara R; National Kagawa Children's Hospital: Ohta A; Ehime Prefectural Central Hospital: Akiyoshi S; St. Mary's Hospital: Shimokawa S; Kitakyushu City Municipal Medical Center: Matsumoto N; Fukuoka University: Oota E; Kumamoto City Hospital: Kondo Y; Okinawa Chubu Hospital: Kohama M.

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Ethical approve

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored. The database was registered as UMIN000006961.

Conflicts of interest

This study was partly supported by a grant from the Ministry of Health, Labour and Welfare, Japan to SK and MF. Thus, the data collection from the participating hospitals was performed by assistants employed under the grand. All information about the infants was collected anonymously, and the data were stored under the responsibility of SK. Other member can access the data after the permission from SK and MF. There was no participation from the funder in the writing and the decision of publication of this manuscript.

Contributorship statement

Satoshi Kusuda (SK), Atushi Uchiyama (AU), Hidehiko Nakanishi (HN), and Satsuki Totsu (ST) participated in data collection. SK, AU, HN, ST and Masanori Fujimura (MF) made the study design and analyzed the data. MF directed statistical analyses. SK mainly worked for interpretation of the results. Thus, all authors participated substantially in the study.

All co-authors had reviewed the draft of the manuscript and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.