



Comparison of Follow-up Courses after Discharge from Neonatal Intensive Care Unit between Very Low Birth Weight Infants with and without Home Oxygen

Ji Sook Kim,^{1*} Jae Won Shim,^{2*}
Jang Hoon Lee,³ Yun Sil Chang,¹
and for the Committee on Data
Collection and Statistical Analysis,
the Korean Society of Neonatology

¹Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; ²Department of Pediatrics, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; ³Department of Pediatrics, Ajou University School of Medicine, Suwon, Korea

*Ji Sook Kim and Jae Won Shim contributed equally to this work.

Received: 13 February 2017

Accepted: 30 April 2017

Address for Correspondence:

Yun Sil Chang, MD, PhD
Department of Pediatrics, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
E-mail: yschang@skku.edu

Funding: This study was supported by a grant (PH01115545) from the Committee on Data Collection and Statistical Analysis of the Korean Society of Neonatology.

INTRODUCTION

Recently advanced neonatal intensive care markedly improved the survival rates of very low birth weight infants (VLBWIs) weighing less than 1,500 g at birth (1). Home oxygen use can facilitate early discharge of survived VLBWIs who experience frequent hypoxic events due to various morbidities, such as bronchopulmonary dysplasia (BPD), apnea-bradycardia of prematurity, and feeding related desaturation (2-5). Home oxygen use in infants also enables bonding with parents in the home environment in addition to promotion of improved growth and development and reduces healthcare costs (6). Home oxygen is usually recommended in infants with oxygen saturations below 92% to 95% in room air (7). However, there is a lack of general consensus regarding home oxygen use in VLBWIs among neonatal intensive care units (NICUs). Moreover, because infants receiving home oxygen are usually expected to have frequent healthcare utilization related to their original morbidities, ap-

In order to investigate the clinical impact of home oxygen use for care of premature infants, we compared the follow-up courses after neonatal intensive care unit (NICU) discharge between very low birth weight infants (VLBWIs) with and without home oxygen. We retrospectively identified 1,232 VLBWIs born at 22 to 32 weeks of gestation, discharged from the NICU of 43 hospitals in Korea between April 2009 and March 2010, and followed them up until April 2011. Clinical outcomes, medical service uses, and readmission and death rates during follow-up after the NICU discharge were compared between VLBWIs with (HO, n = 167) and those without (CON, n = 1,056) home oxygen at discharge. The HO infants comprised 13.7% of the total VLBWIs with significant institutional variations and showed a lower gestational age (GA) and birth weight than the CON infants. The HO infants had more frequent regular pediatric outpatient clinic visits (12.7 ± 7.5 vs. 9.5 ± 6.6 ; $P < 0.010$) and emergency center visits related to respiratory problems (2.5 ± 2.2 vs. 1.8 ± 1.4 ; $P < 0.010$) than the CON infants. The HO infants also had significantly increased readmission (adjusted hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.25–2.04) and death risks (adjusted HR, 7.40; 95% CI, 2.06–26.50) during up to 2 years following the NICU discharge. These increased readmission and death risks in the HO infants were not related to their prematurity degree. In conclusion, home oxygen use after discharge increases the risks for healthcare utilization, readmission, and death after NICU discharge in VLBWIs, regardless of GA, requiring more careful health care monitoring during their follow-up.

Keywords: Infants; Premature; Oxygen; Prognosis; Readmission; Death

propriate follow-up plans after NICU discharge must be established, with basic knowledge regarding their follow-up courses (8,9). However, to date, there are no actual data regarding home oxygen use in VLBWIs discharged from the NICU in Korea. Therefore, the prevalence as well as the real effect of home oxygen use in VLBWIs on health care utilization during follow-up periods after NICU discharge needs to be investigated urgently for the proper provision of their national health care monitoring.

A large national retrospective survey for health care utilization after NICU discharge in preterm infants below 33 weeks of gestation “Retrospective Study to Evaluate Rehospitalization & Health Care Utilization after NICU Discharge in Preterm Infant of < 33 weeks’ gestation (RHANPI) study” in Korea has been previously conducted and confirmed that preterm infants were more prone to readmission following NICU discharge in Korea (10). Using the part of these data, we aimed to evaluate the prevalence of home oxygen use and to analyze the clinical impact of home oxygen use in VLBWIs on their healthcare utilization, re-

admission, and death following NICU discharge by comparison between those of VLBWI with and without home oxygen at NICU discharge.

MATERIALS AND METHODS

The study population consisted of VLBWIs who were born < 1,500 g and 22 to 32 weeks' gestation at birth and survived to NICU discharge between April 2009 and March 2010, and were followed up until April 2011. Data used in this study were collected between August and December 2011 through the national survey of the RHANPI study conducted by the Committee on Data Collection and Statistical Analysis of the Korean Society of Neonatology. The RHANPI dataset originally included 2,351 preterm infants who were born at 22 to 32 weeks' gestation and survived to discharge from April 2009 to March 2010 from 44 participating institutions in Korea (10).

Among 2,351 preterm infants 1,356 VLBWIs from 43 hospitals (1 hospital with no VLBWI was excluded), who weighed < 1,500 g at birth, were identified for this study, and 124 cases that had missing data on home oxygen use were excluded. Finally, 1,232 VLBWIs were identified and divided into groups of infants prescribed with (HO, $n = 167$) and without (CON, $n = 1,059$) home oxygen at discharge. Perinatal and neonatal outcomes were compared between the 2 groups. Clinical effects of home oxygen use in VLBWIs were analyzed by comparison of the rate and frequency of outpatient department (OPD) and emergency room (ER) visits and readmission and death rate following NICU discharge between the 2 groups. These comparisons were conducted in total and stratified gestational age (GA)-subgroups of 25 weeks' gestation or less ($\leq 25w$ GA), of 26–28 weeks' gestation (26–28w GA), and of 29 weeks' gestation or more ($\geq 29w$ GA).

Based on standard study formats and manual definition of the RHANPI study variables, the neonatologists at each center retrospectively collected data by reviewing charts and registered all information in a central database between August and December 2011. To improve data quality, collected data were reviewed repeatedly, and all data that had suspected errors or missing information were referred to the corresponding neonatologist for correction. A central database of the electronic case reporting system of Oracle Korea (Oracle Corporation, Seoul, Korea) was created in collaboration with the Clinical Research Center of Samsung Medical Center.

GA at birth was determined by the best obstetric estimate, using the last menstrual period or early ultrasonographic examination (11). Small for GA was defined as birth weight less than the 10th percentile for GA compared with the intrauterine preterm growth chart (12). Grade III or IV intraventricular hemorrhage (IVH) was diagnosed using cranial ultrasonography and classified in accordance with the grading system of Papile et al. (13). Necrotizing enterocolitis (NEC) was defined as Bell's

stage II or greater (14). BPD was defined as the need for supplemental oxygen at 36 postmenstrual weeks or discharge, whichever came first (15).

Home oxygen was recorded when the infants were discharged home with oxygen use of any type of support. At discharge, whether the infants required a home pulse oximetry (monitor) or G-tube or gastrostomy tube feeding were also recorded. Duration of home oxygen use was recorded.

OPD visits were defined as pediatric outpatient clinic visits and comprised regular and irregular visits. Regular visits were prearranged visits to monitor growth and development or for vaccination, and irregular visits were unscheduled visits for a check-up for various health issues including respiratory problems. Readmission after NICU discharge was defined as readmission to any hospital as stated in the patient's medical records. Visits to emergency centers and outpatient clinics were confined to events at the participating hospitals.

Statistical analysis

Continuous data were presented as means and standard deviations and categorical data as actual numbers and percentages. For between-group comparisons, the Student's *t*-test was used for continuous variables and the χ^2 test for categorical variables. The Pearson correlation was analyzed between the proportion of home oxygen use and number of VLBWIs discharged alive in each hospital. The Kaplan-Meier estimation was used to estimate the cumulative readmission rate after NICU discharge, and the log-rank test was used to compare the readmission rate following NICU discharge between the 2 groups or among GA sub-groups. To analyze the risks for readmission or death rate, we used the time-dependent Cox proportional hazard model with the following covariates: home oxygen use, GA and follow-up duration. The hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values were reported. All *P* values < 0.05 were considered statistically significant. All analyses were performed using the SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Ethics statement

The Institutional Review Board (IRB) of Samsung Medical Center and of each of the 42 other participating hospitals approved this study (IRB No. 2016-11-128). Informed consent was waived by the IRB.

RESULTS

Home oxygen use and institutional variation

The proportion of HO in the VLBWIs clearly showed significant institutional variation (Fig. 1). Of 43 hospitals enrolled, the proportion of HO in VLBWIs was 0% in 14 hospitals and ranged from 2.9% to 36.4% in 29 hospitals. The mean number of VLBWIs discharged alive from the enrolled 43 hospitals was $28.7 \pm$

22.0 (range, 7–121), and the mean proportion of home oxygen use in each hospital was $10.6\% \pm 11.2\%$. There was no significant correlation between the proportion of home oxygen use and the total number of VLBWIs discharged alive in each hospital ($R^2 = 0.1412$; $P > 0.050$) (Fig. 1).

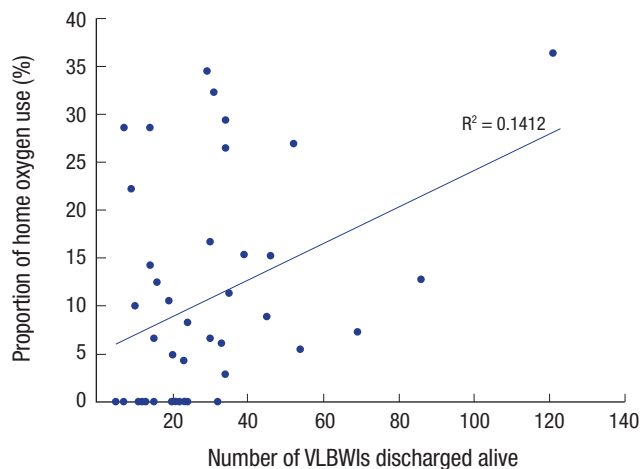


Fig. 1. Correlation of number of VLBWIs discharged alive with the proportion of home oxygen use. Correlation of number of VLBWIs discharged alive with the proportion of home oxygen use in each hospital, which showed no significant correlation ($R^2 = 0.1412$; $P > 0.050$). Fourteen hospitals showed 0% home oxygen use in VLBWIs discharged alive and 29 hospitals showed the proportion of home oxygen use ranged from 2.9% to 36.0%. VLBWIs = very low birth weight infants.

Clinical characteristics and follow-up duration

Comparisons of the clinical characteristics and follow-up duration after NICU discharge between the HO and CON in total and in each GA subgroup were described in Table 1. The proportion of the HO infants was 13.7% in total, 37.1% in the $\leq 25w$ GA (49/132), 17.5% in the 26–28w GA (87/497), and 5.5% in the $\geq 29w$ GA subgroup (44/431).

The mean GA and birth weight were significantly lower in the HO infants than in the CON infants in total and in all GA subgroups, respectively. The proportion of male infants among the enrolled infants was higher in the HO infants than in the CON infants in total and in $\geq 29w$ GA subgroup. Antenatal steroid use was higher in the HO infants than in the CON infants in total, but not in all GA subgroups. There were no differences between the 2 groups in the proportion of SGA and of having elder siblings. More use of surfactants and higher rates of high grade IVH and blood culture-proven sepsis were observed in the HO infants than in the CON infants, in total. The HO infants comprised more infants diagnosed with BPD than the CON infants in total and in all of GA subgroups.

The follow-up duration was not equal between the 2 groups. The mean follow-up duration of infants after NICU discharge was slightly longer in the HO infants than in the CON infants. However, follow-up loss during the relatively early period (less than 12 months after discharge) was frequent in the HO infants, especially in subgroups of 26–28w GA and $> 29w$ GA.

The mean duration of home oxygen use in the $\leq 25w$ GA subgroup was longer than that in the 26–28w GA subgroup, which

Table 1. Clinical characteristics, outcome, and follow-up duration of VLBWIs with and without home oxygen use

Characteristics	Total		$\leq 25w$ GA		26–28w GA		$\geq 29w$ GA	
	HO (n = 169)	CON (n = 1,063)	HO (n = 49)	CON (n = 83)	HO (n = 87)	CON (n = 410)	HO (n = 33)	CON (n = 570)
GA, wk	26.7 \pm 2.0	28.6 \pm 2.0*	24.3 \pm 0.8	24.7 \pm 0.5*	26.9 \pm 0.8	27.2 \pm 0.0*	29.6 \pm 0.7	30.2 \pm 1.0*
Birth weight, g	958 \pm 247	1,135 \pm 229*	740 \pm 132	800 \pm 124*	1,006 \pm 216	1,061 \pm 195*	1,158 \pm 222	1,237 \pm 515*
Male	99 (58.6)	498 (46.8)*	28 (57.1)	45 (54.2)	48 (55.2)	199 (48.5)	23 (69.7)	254 (44.6)*
Antenatal steroid	109 (68.1)	748 (70.4)*	29 (59.2)	60 (72.3)	56 (64.4)	293 (71.5)	24 (72.7)	395 (69.3)
Small for GA	19 (11.2)	149 (14.0)	2 (4.1)	4 (4.8)	9 (10.3)	27 (6.6)	8 (24.2)	118 (20.7)
Elder siblings	57 (33.7)	404 (38.0)	14 (28.6)	30 (36.1)	29 (33.3)	170 (41.5)	14 (42.4)	204 (35.8)
Use of surfactant	143 (84.6)	693 (65.2)*	47 (95.9)	71 (85.5)	73 (83.9)	313 (76.3)*	23 (69.7)	309 (54.2)
NEC (\geq stage 2)	16 (9.5)	62 (5.8)	6 (12.2)	10 (12.0)	7 (8.0)	30 (7.3)	3 (9.1)	22 (3.9)
IVH (\geq grade 3)	11 (6.5)	19 (1.8)*	5 (10.2)	5 (6.0)	5 (5.7)	10 (2.4)	1 (3.0)	4 (0.7)
BPD (moderate to severe)	82 (48.5)	150 (14.1)*	29 (59.2)	34 (41.0)*	37 (47.5)	77 (18.8)*	16 (48.5)	39 (6.8)*
Culture proven sepsis	38 (22.5)	188 (17.7)*	17 (34.7)	31 (37.3)	17 (19.5)	89 (21.7)	4 (12.1)	68 (11.9)
Follow-up duration, day	744 \pm 179	715 \pm 120*	760 \pm 166	710 \pm 118	758 \pm 169	719 \pm 121*	701 \pm 216	713 \pm 120
Follow-up (> 12 mon)	5 (3.0)	5 (0.5)*	2 (2.3)	0 (0.0)	2 (2.3)	1 (0.2)*	2 (6.1)	4 (0.7)*
Duration of home oxygen use, day	69 \pm 99	-	90 \pm 118	-	65 \pm 98	-	47 \pm 58	-
Home oximetry use	163 (96.4)	112 (10.5)*	49 (100.0)	21 (25.3)*	84 (96.6)	54 (13.2)*	30 (90.9)	37 (6.5)*
G-tube or gastrostomy at discharge	48 (28.4)	13 (1.2)*	12 (24.5)	2 (2.4)*	28 (32.2)	6 (1.5)*	8 (24.2)	5 (0.9)*

Data shown are number (%) not otherwise specified.

VLBWIs = very low birth weight infants, $\leq 25w$ GA = gestational age-subgroup of 25 weeks' gestation or less, 26–28w GA = gestational age-subgroup of 26–28 weeks' gestation, $\geq 29w$ GA = gestational age-subgroup of 29 weeks' gestation or more, HO = home oxygen use at discharge, CON = no home oxygen use at discharge, GA = gestational age, NEC = necrotizing enterocolitis, IVH = intraventricular hemorrhage, BPD = bronchopulmonary dysplasia.

* $P < 0.050$ vs. HO.

was longer than that of in the ≥ 29 w GA subgroup. The proportion of home pulse oximetry use and G-tube/gastrostomy feeding at discharge was higher in the HO infants than in the CON infants in total and in all of the GA subgroups.

Medical service uses and death during follow-up after NICU discharge

We compared the follow-up courses by focusing on use of medical services, such as pediatric OPD visits, ER visits, and readmission, and on death following discharge between the 2 groups (Table 2).

Because the total mean follow-up duration after discharge was longer (743 ± 179 vs. 715 ± 120 days; $P < 0.050$) and the GA was lower in the HO infants than in the CON infants, adjusted odds ratios (ORs) or HRs for medical service use or death of the HO infants compared to the CON infants were calculated by correction of the follow-up duration and GA of the infants (Table 3).

Most of the VLBWIs visited a pediatric OPD after NICU discharge. The proportion of the infants who visited pediatric OPD regularly more than once was significantly lower in the HO infants than in the CON infants in total (85.2% vs. 95.7%; $P < 0.001$; adjusted OR, 0.26; 95% CI, 0.44–0.60) and in all GA subgroups. However, the HO infants more frequently went to regular OPDs for check-ups on growth and development and for vaccinations compared to the CON infants (12.7 ± 7.5 vs. 9.5 ± 6.6 times; $P < 0.010$). The total percentage of infants who visited an ER for any reason after NICU discharge was not significantly different between the HO and CON infants (37.3% vs. 31.9%; $P > 0.05$; adjusted OR, 1.25; 95% CI, 0.89–1.75); the proportion of infants with ER visits owing to respiratory problems was higher in total (22.8% vs. 19.1%; $P < 0.050$; adjusted OR, 1.47; 95% CI, 0.99–2.16), with modest significance, and with a significance in the 26–28w GA subgroup. Furthermore, ER visits owing to respiratory problems were more frequent in the HO infants than in the CON infants in total (2.5 ± 2.2 vs. 1.8 ± 1.4 times; $P < 0.050$).

The overall rate of readmission for any reason in the HO infants was significantly higher than that in the CON infants in total (53.3% vs. 35.7%; $P < 0.010$) and in ≥ 29 w GA subgroup. The overall death rate was also significantly higher in the HO infants than in the CON infants in total (3.0% vs. 0.6%; $P < 0.050$) and in the ≥ 29 w GA subgroup (6.1% vs. 0.7%; $P < 0.05$). The adjusted HR for death in the HO infants was 7.40 (95% CI, 2.06–26.50) in total, 4.75 (95% CI, 0.67–33.71) in the 26–28w GA subgroup, and 8.94 (95% CI, 1.64–48.79) in the ≥ 29 w GA subgroup respectively.

Cumulative readmission rate

The cumulative readmission rates at the time-point after discharge from the NICU are shown in Table 4. In the first 360 days after discharge from the NICU, 46.1% of the HO infants readmitted cumulatively in total, 56.3% in the ≤ 25 w GA subgroup,

Table 2. Medical resources used and death between VLBWIs with and without home oxygen use

Medical services	Total						≤ 25 w GA						≥ 29 w GA					
	HO (n = 169)		CON (n = 1,063)		HO (n = 49)		CON (n = 83)		HO (n = 87)		CON (n = 410)		HO (n = 33)		CON (n = 570)			
	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD	No. (%)	Mean \pm SD		
OPD visit	144 (85.2)	15.7 \pm 11.1	1,017 (95.7)*	12.9 \pm 10.0*	40 (81.6)	16.7 \pm 9.7	80 (96.4)*	16.9 \pm 12.0	75 (86.2)	16.1 \pm 12.4	392 (95.6)*	14.2 \pm 10.8	29 (87.9)	13.2 \pm 8.9	545 (95.6)*	11.4 \pm 8.6		
Regular visit	133 (78.7)	12.7 \pm 7.5	1,001 (98.7)*	9.5 \pm 6.6*	38 (77.6)	13.6 \pm 7.7	78 (94.0)*	12.0 \pm 7.2	67 (77.0)	12.9 \pm 7.9	385 (93.9)*	10.4 \pm 7.2*	28 (84.8)	10.7 \pm 6.0	538 (94.4)	8.5 \pm 5.8*		
Irregular visit	108 (63.9)	5.3 \pm 4.0	660 (62.1)	5.6 \pm 6.7	27 (55.1)	5.6 \pm 5.0	60 (72.3)	7.0 \pm 9.8	61 (70.1)	5.6 \pm 8.3	268 (65.4)	5.9 \pm 6.8	20 (60.6)	4.1 \pm 4.2	332 (58.2)	5.1 \pm 5.9		
Respiratory	85 (50.3)	4.8 \pm 6.7	497 (46.8)	4.9 \pm 5.6	21 (42.9)	4.7 \pm 3.9	48 (57.8)	5.3 \pm 5.6	49 (56.3)	5.0 \pm 8.2	213 (52.0)	5.3 \pm 6.3	15 (45.5)	3.9 \pm 3.2	236 (41.4)	4.4 \pm 4.7		
Non-respiratory	68 (40.2)	2.5 \pm 2.1	420 (39.5)	3.0 \pm 4.4	19 (38.8)	2.7 \pm 2.1	39 (47.0)	4.2 \pm 8.6	39 (44.8)	2.4 \pm 2.2	168 (41.0)	2.7 \pm 3.2	10 (30.3)	2.3 \pm 1.8	213 (37.4)	3.0 \pm 4.0		
ER visit	63 (37.3)	3.0 \pm 2.7	339 (31.9)	2.2 \pm 2.0*	19 (38.8)	2.7 \pm 2.0	29 (34.9)	2.7 \pm 2.2	33 (37.9)	3.0 \pm 2.8	134 (32.7)	2.2 \pm 2.1	11 (33.3)	3.5 \pm 3.4	176 (30.9)	2.1 \pm 1.8		
Respiratory	47 (22.8)	2.5 \pm 2.2	203 (19.1)*	1.8 \pm 1.4*	11 (22.4)	2.0 \pm 1.5	20 (24.1)	2.2 \pm 1.4	29 (33.3)	2.3 \pm 2.2	86 (21.0)	1.8 \pm 1.3	7 (21.2)	4.1 \pm 3.0	97 (17.0)	1.8 \pm 1.4		
Non-respiratory	36 (21.3)	1.9 \pm 1.4	230 (21.6)	1.6 \pm 1.2	13 (26.5)	2.2 \pm 2.0	20 (24.1)	1.8 \pm 1.3	16 (18.4)	1.9 \pm 1.0	88 (21.5)	1.6 \pm 1.4	7 (21.2)	1.4 \pm 0.5	122 (21.4)	1.6 \pm 1.0		
Readmission	90 (53.3)	1.9 \pm 1.7	380 (35.7)*	1.9 \pm 1.6	29 (59.2)	2.1 \pm 1.9	39 (47.0)	2.5 \pm 2.4	44 (50.6)	1.9 \pm 1.6	160 (39.0)	2.0 \pm 1.6	17 (51.5)	1.7 \pm 1.6	181 (31.8)*	1.8 \pm 1.4		
Respiratory	51 (30.2)	1.9 \pm 1.4	202 (19.0)	1.7 \pm 1.3	20 (40.8)	1.7 \pm 1.1	19 (22.9)	2.4 \pm 1.7	25 (28.7)	1.9 \pm 1.3	94 (22.9)	1.6 \pm 1.1	6 (18.2)	2.8 \pm 2.3	89 (15.6)	1.6 \pm 1.2		
Non-respiratory	56 (33.1)	1.3 \pm 1.2	244 (23.0)	1.6 \pm 1.3	16 (32.7)	1.7 \pm 2.0	29 (34.9)	1.8 \pm 2.2	29 (33.3)	1.2 \pm 0.8	99 (24.1)	1.7 \pm 1.3*	11 (33.3)	1.1 \pm 0.3	116 (20.4)	1.5 \pm 0.8*		
Death	5 (3.0)	-	6 (0.6)*	-	1 (2.0)	-	0 (0.0)	-	2 (2.3)	-	2 (0.5)	-	2 (6.1)	-	4 (0.7)*	-		

VLBWIs = very low birth weight infants, ≤ 25 w GA = gestational age-subgroup of 25 weeks' gestation or less, 26–28w GA = gestational age-subgroup of 26–28 weeks' gestation, ≥ 29 w GA = gestational age-subgroup of 29 weeks' gestation or more, HO = home oxygen use at discharge, CON = no home oxygen use at discharge, SD = standard deviation, OPD = outpatient department, ER = emergency room. * $P < 0.050$ vs. HO.

Table 3. Risks of medical resources used and death between VLBWIs with and without home oxygen use

Risks of medical resources	OPD visit		ER visit		Death	
	Total	Regular	Total	Respiratory	Crude HR (95% CI)	Adjusted HR (95% CI)
Crude OR (95% CI)						
HO	0.26 (0.44–0.6)	0.23 (0.15–0.36)	1.25 (0.89–1.75)	1.61 (1.11–2.33)	5.32 (1.62–17.42)	-
CON/P value	1 (ref)/ < 0.001	1 (ref)/ < 0.001	1 (ref)/0.201	1 (ref)/0.012	1 (ref)/0.006	-
Adjusted OR (95% CI)						
Total						
HO	0.27 (0.15–0.47)	0.25 (0.15–0.40)	1.19 (0.84–1.70)	1.47 (0.99–2.16)	-	7.40 (2.06–26.50)
CON/P value	1 (ref)/ < 0.001	1 (ref)/ < 0.001	1 (ref)/0.334	1 (ref)/0.054	-	1 (ref)/0.002
≤ 25w GA						
HO	0.17 (0.04–0.65)	0.22 (0.07–0.68)	1.16 (0.56–2.41)	0.90 (0.39–2.08)	-	-*
CON/P value	1 (ref)/0.010	1 (ref)/0.009	1 (ref)/0.695	1 (ref)/0.800	-	1 (ref)
26–28w GA						
HO	0.28 (0.13–0.61)	0.23 (0.12–0.44)	1.24 (0.76–2.01)	1.76 (1.05–2.95)	-	4.75 (0.67–33.71)
CON/P value	1 (ref)/0.001	1 (ref)/ < 0.001	1 (ref)/0.389	1 (ref)/0.031	-	1 (ref)/0.119
≥ 29w GA						
HO	0.33 (0.11–1.02)	0.33 (0.12–0.92)	1.10 (0.52–2.31)	1.29 (0.55–3.06)	-	8.94 (1.64–48.79)
CON/P value	1 (ref)/0.054	1 (ref)/0.034	1 (ref)/0.808	1 (ref)/0.562	-	1 (ref)/0.011

VLBWIs = very low birth weight infants, OPD = outpatient department, ER = emergency room, HR = hazard ratio, OR = odds ratio, HO = home oxygen use at discharge, CON = no home oxygen use at discharge, CI = confidence interval, ≤ 25w GA = gestational age-subgroup of 25 weeks' gestation or less, 26–28w GA = gestational age-subgroup of 26–28 weeks' gestation, ≥ 29w GA = gestational age-subgroup of 29 weeks' gestation or more.

*Unavailable due to 0 events in CON.

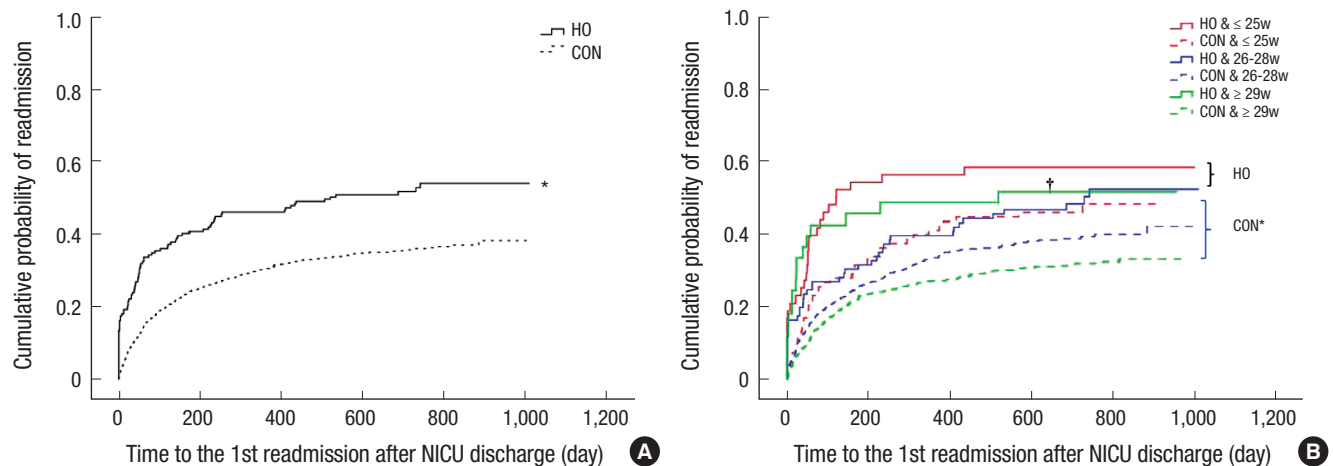


Fig. 2. Cumulative probability of readmission of enrolled infants after NICU discharge. Cumulative probability of readmission of enrolled infants depicted by time to the first readmission after NICU discharge in total (A) and according to GA subgroups (B). In total (A), the HO subgroup significantly higher probability of readmission than that of the CON subgroup in VLBWIs discharged alive from NICU. In subgroup analysis (B), whereas there were significant differences in cumulative probability or readmission among CON subgroups, no differences were found among HO subgroups.

NICU = neonatal intensive care unit, GA = gestational age, HO = home oxygen use at discharge, CON = no home oxygen use at discharge, VLBWIs = very low birth weight infants, ≤ 25w GA = gestational age-subgroup of 25 weeks' gestation or less, 26–28w GA = gestational age-subgroup of 26–28 weeks' gestation, ≥ 29w GA = gestational age-subgroup of 29 weeks' gestation or more.

* $P < 0.050$ by log-rank test; † $P < 0.050$ by log-rank test between the HO and the CON in ≥ 29w GA subgroup.

39.5% in the 26–28w GA, and 48.5% in the ≥ 29w GA subgroup; 30.6% of the CON infants readmitted in total, 41.0%, 33.4%, and 27.1% in each GA subgroup, respectively. Consequently, the HO infants showed a significantly higher probability of total readmissions compared to the CON infants in total (Fig. 2A) (log-rank test for trend < 0.05) and in any GA subgroups, except for the ≤ 25w GA subgroup (Table 4). In addition, the HO infants did not show significant differences in the cumulative readmission rate calculated by log-rank among the GA subgroups, where-

as the CON infants showed significant differences (Fig. 2B). Consequently, the degree of prematurity proportionally increase the risk for readmission in the CON infants; this trend was not observed in the HO infants.

DISCUSSION

The present study has demonstrated that 13.7% of total VLBWIs identified nationally have been discharged from the NICU, with

Table 4. Cumulative readmission rate after discharge from NICU between VLBWIs with and without home oxygen use

Classifications	Total	Readmission	Censored	Cumulative readmission rate			Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value	
				At 90 days (95% CI)	At 180 days (95% CI)	At 360 days (95% CI)					At 720 days (95% CI)
Total	167	88 (52.7)	79 (47.3)	35.3 (28.1-42.6)	40.7 (33.3-48.2)	46.1 (38.6-53.7)	51.5 (43.9-59.1)	1.802 (1.428-2.272)	< 0.001	1.595 (1.249-2.038)	< 0.001
HO	1,059	378 (35.7)	681 (64.3)	17.6 (15.3-19.9)	24.6 (22.0-27.1)	30.6 (27.8-33.4)	35.1 (32.3-38.0)	1 (ref)		-	
CON	1,226	466 (38.0)	760 (62.0)	20.0 (17.8-22.2)	26.8 (24.3-29.2)	32.7 (30.1-35.3)	37.4 (34.7-40.1)	-		-	
≤ 25w GA	48	28 (58.3)	20 (41.7)	45.8 (31.7-59.9)	54.2 (40.1-68.3)	56.3 (42.2-70.3)	58.3 (44.4-72.3)	1.551 (0.953-2.522)	0.077	1.551 (0.953-2.522)	0.077
HO	83	39 (47.0)	44 (53.0)	25.3 (16.0-34.7)	31.3 (21.4-41.3)	41.0 (30.4-51.5)	45.8 (35.1-56.5)	1 (ref)		1 (ref)	
CON	131	67 (51.1)	64 (48.9)	32.8 (24.8-40.9)	39.7 (31.3-48.1)	46.6 (38.0-55.1)	50.4 (41.8-58.9)	-		-	
26-28w GA	86	43 (50.0)	43 (50.0)	26.7 (17.4-36.1)	31.4 (21.6-41.2)	39.5 (29.2-49.9)	47.7 (37.1-58.2)	1.397 (0.997-1.956)	0.052	1.408 (1.002-1.979)	0.049
HO	407	159 (39.1)	248 (60.9)	19.2 (15.3-23.0)	25.6 (21.3-29.8)	33.4 (28.8-38.0)	38.3 (33.6-43.1)	1 (ref)		-	
CON	493	202 (41.0)	291 (59.0)	20.5 (16.9-24.1)	26.6 (22.7-30.5)	34.5 (30.3-38.7)	40.0 (35.6-44.3)	-		-	
≥ 29w GA	33	17 (51.5)	16 (48.5)	42.4 (25.6-59.3)	45.5 (28.5-62.4)	48.5 (31.4-65.5)	51.5 (34.5-68.6)	2.222 (1.351-3.654)	0.002	2.222 (1.351-3.654)	0.002
HO	569	180 (31.6)	389 (68.4)	15.3 (12.3-18.3)	22.9 (19.4-26.3)	27.1 (23.4-30.7)	31.3 (27.5-35.1)	1 (ref)		1 (ref)	
CON	602	197 (33.7)	405 (67.3)	16.8 (13.8-19.8)	24.1 (20.7-27.5)	28.2 (24.6-31.8)	32.4 (28.7-36.1)	-		-	

NICU = neonatal intensive care unit, VLBWIs = very low birth weight infants, CI = confidence interval, HR = hazard ratio, HO = home oxygen use at discharge, CON = no home oxygen use at discharge, ≤ 25w GA = gestational age-subgroup of 25 weeks' gestation or less, 26-28w GA = gestational age-subgroup of 26-28 weeks' gestation, ≥ 29w GA = gestational age-subgroup of 29 weeks' gestation or more, GA = gestational age. *P value was adjusted for the GA and the duration of follow-up.

home oxygen showing significant institutional variations in Korea. These infants were more likely to be born at a younger GA and to need more a G-tube or gastrostomy at discharge. The VLBWIs with home oxygen visited regular pediatric OPD and ER owing to respiratory problems more frequently and had the increased the risk of 1.6 times for re-admission and 7.4 times for death compared to VLBWIs without home oxygen. However, these increased risks in the VLBWIs with home oxygen were not significantly related to their degree of prematurity. Consequently, home oxygen use in the VLBWIs increased the risks for their readmission and the use of medical services as well as for death following discharge from the NICU, which necessitate the proper provision of a more carefully planned health care monitoring.

Recently, the prevalence of home oxygen use by preterm infants at NICU discharge is increasing, as evident in the study from Australia showing that the percentage of home oxygen use in preterm infants increased from 2.3% in the 1980s to 10% in the early 2000s (16). In a study from the United States, 16.6% of preterm infants with 23-31 weeks of GA used home oxygen after discharge, which is consistent with our results. In that study, the rate ranged from 59.2% of those with GA < 25 weeks to 7.3% of those with ≥ 29 weeks (17). The EPICure study showed that of the 283 survivors born at ≤ 25 weeks' gestation, 36% were discharged home on oxygen (18), which is also consistent with the rate of 37.1% of the infants born at ≤ 25 weeks' gestation in the present study. The rate of home oxygen use in the VLBWIs was inversely proportional to GA, which ranged from 37.1% in the infants born at ≤ 25 weeks' gestation to 5.5% in the infants born at ≥ 29 weeks in the present study. In summary, these findings suggest that a certain proportion of immature preterm infants necessitate HO as these infants tend to survive more.

Institutional variation might be the most important factor for the determination of home oxygen use in preterm infants (17). In the present study, the rate of home oxygen use ranged from 2.9% to 36.4% in 29 NICUs as well as even 0% in 14 NICUs. A German study reported that NICUs admitting > 50 VLBWIs annually significantly and more frequently prescribed home oxygen and aimed for SpO₂ levels closer to the physiological range than those admitting fewer VLBWIs (19). However, in the present study, we could not find any correlation for NICU size and prescription rate of home oxygen at discharge in the VLBWIs. Further studies are needed to elucidate the exact effect of institutional variation on the rate of home oxygen use in preterm infants in Korea.

Home oxygen use enables early discharge from the NICU and reduces the risk of exposure to an adverse environment resulting from a prolonged hospital stay; this also reduces medical expenses, allows efficient use of medical resources, and is beneficial for a closer parent-infant relationship (16,20,21). In contrast, home oxygen therapy increases parental stress from

the use of medical equipment at home, and home care of the infant may increase the risks of various aspects such as vulnerable lung function (22-24), which necessitate careful monitoring and follow-up plan.

Therefore, the present study has attempted to examine how the follow-up courses after NICU discharge were affected by home oxygen use among the VLBWIs by comparison with the VLBWIs without home oxygen use. Unexpectedly, even after adjustments of the different follow-up durations and GA of the 2 groups, the percentage of infants who visited regular outpatient clinics in the HO infants was significantly lower than that in the CON infants. This might be resulted from more early follow-up loss in HO group than in CON group, which was demonstrated that the proportion of the infants with follow-up loss within 12 months for discharge was significantly higher in HO group than in CON group. Our study retrospectively surveyed NICU of various sizes. Therefore, at smaller NICU, some infants with more complicated courses such as development of severe retinopathy of prematurity (ROP), complicated surgical, or respiratory problems, who probably comprised a higher proportion of the infants in the HO group than in the CON group, might have been transferred to larger hospitals during follow-up after NICU discharge. Furthermore, since visits to OPD were confined to events at the participating hospitals in the present study, inconvenience for moving due to oxygen supply in HO group might have been a factor for impeding regular visits to participating hospital and thus for favoring visits to their vicinity hospital. This lower rate of regular pediatric OPD visits in the home oxygen group needs to be re-examined via prospectively designed studies in the future.

On the other hand, in the present study, the frequency of regular outpatient visits was greater in the HO group, whereas the frequency of irregular visits, including those for respiratory problems, was not different between the groups. This is probably because the proportion of the patients with BPD was significantly higher in the HO group than the CON group, and they were main candidates for respiratory syncytial virus (RSV) prophylaxis, which needed regular follow-up at least once a month during RSV seasons (23,25,26). In contrast, Spiegler et al. (27) reported that in a follow-up of VLBWIs for a year after discharge, the difference in the number of outpatient visits was smaller than expected because the schedule of vaccinations and regular check-ups during the first year was tight for all VLBWIs.

Our study demonstrated 1.6 times higher risks for readmission in the HO group compared to that in the CON group without significant correlation between the readmission risks and degree of prematurity in the home oxygen group. This result was consistent with that of a prospective study on respiratory outcomes following extreme preterm birth in England, which demonstrated that children discharged with home oxygen were at an increased risk for readmission in the first 30 months (18).

Furthermore, in the present study, 3.0% of the HO group (5/169) died after discharge during the follow-up period; this group also had a higher risk of death by 7.4 times following NICU discharge than the CON group. Although we were unable to collect data on the causes of death, the main causes of death for these high-risk newborn infants might include respiratory infection, respiratory failure, and cor pulmonale during home care (28), which can be confirmed in further prospective studies in the future.

Notably, in the present study, the degree of prematurity did not correlated with increased risks of readmission or death in the VLBWIs with home oxygen. Therefore, we must carefully consider the decision for discharge with home oxygen in these high-risk infants and require meticulous education of parents regarding home cardiopulmonary monitoring as well as planned and careful health care follow-up.

There are several limitations in our study. A retrospective nature has major drawbacks. With data collected for the cases prior to the design of this study, detailed information regarding home oxygen use and weaning during follow-up as well as heterogeneous underlying diseases, was unavailable. The number of visits and duration of follow-up after discharge were different among the infants. The effects of institutional variation, such as prescription guidelines for home oxygen use and follow-up schedules in preterm infants, could not be analyzed because of the lack of information. Despite these several limitations, the strength of our report would be that it is the first large-scale, nationwide report on VLBWIs with home oxygen and their follow-up courses in Korea.

In conclusion, approximately 13% of all survived VLBWIs require home oxygen at discharge from NICUs in Korea. Less mature infants are more prone to be prescribed with home oxygen at discharge. Home oxygen use in VLBWIs increased the risks for more use of healthcare facilities following NICU discharge, such as regular OPD or ER visits owing to respiratory problems, as well as for readmission and death during follow-up, regardless of the GA. Therefore, meticulous healthcare monitoring of VLBWIs who require home oxygen after discharge from the NICU is needed, and if possible, development of a special national healthcare program for these patients is required.

ACKNOWLEDGMENT

We thank Hae Sook Bok and Sun Hee Kim for developing the case report form and validating the data. We thank Kyungjoo Kim for performing the statistical analysis and Ye Kyuonng Kwon for developing the electronic case reporting system. We thank Dr. Myo Jing Kim, Young Don Kim, Eun Sun Kim, Eun Song Song, Soon Min Lee, Jin A Lee, Mea young Chang, Hyun Seung Jin, Jong Hee Hwang for helping data collection.

We express our profound gratitude to the physicians at the

institutions that participated in this study. These institutions were as follows: Ajou University Hospital, Asan Medical Center, Boramae Medical Center, Bundang Cha Hospital, Busan National University Hospital, Busan National University Children's Hospital, Gachon University Gil Medical Center, Cheil General Hospital & Women's Healthcare Center, Chonbuk National University Hospital, Chonnam National University Hospital, Chungnam National University Hospital, Daegu Fatima Hospital, Eulji University Hospital, Dankook University Hospital, Dong-A University Hospital, Dongguk University Ilsan Hospital, Ewha Woman's University Mokdong Hospital, Gangneung Asan Hospital, Good Moonhwa Hospital, Gyeongsang National University Hospital, Hallym University Kangnam Sacred Heart Hospital, Hanyang University Guri Hospital, Inje University Busan-Paik Hospital, Inje University Ilsan-Paik Hospital, Inje University Sanggye-Paik Hospital, Jeju National University Hospital, Cha Gangnam Medical Center, Kangwon National University Hospital, Keimyung University Dongsan Medical Center, Konkuk University Medical Center, Korea University Ansan Hospital, Kosin University Gospel Hospital, Kyung Hee University Medical Center at Gangdong, Kyungpook National University Hospital, Samsung Changwon Hospital, Samsung Medical Center, Seoul National University Bundang Hospital, Seoul National University Children's Hospital, Seoul St. Mary's Hospital of the Catholic University of Korea, Soonchunhyang University Cheonan Hospital, St. Mary's Hospital of the Catholic University of Korea, Yonsei University Gangnam Severance Hospital, Yonsei University Severance Hospital, and Yonsei University Wonju Christian Hospital.

AUTHOR CONTRIBUTION

Conceptualization: Kim JS, Lee JH, Chang YS. Data curation: Kim JS, Lee JH. Formal analysis: Kim JS, Shim JW, Chang YS. Writing - original draft: Kim JS, Shim JW. Writing - review & editing: Kim JS, Shim JW, Chang YS.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

ORCID

Ji Sook Kim <https://orcid.org/0000-0002-0100-5845>
 Jae Won Shim <https://orcid.org/0000-0003-0101-3076>
 Jang Hoon Lee <https://orcid.org/0000-0003-4765-9948>
 Yun Sil Chang <https://orcid.org/0000-0001-9201-2938>

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