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Original Article

The Use of Diuretics in Infants with Established or Evolving Bronchopulmonary Dysplasia and Its Impact on the Duration of Home Oxygen Therapy

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Abstract

OBJECTIVE: Bronchopulmonary dysplasia (BPD), defined according to the level of respiratory support and supplemental oxygen administered at 36 weeks postmenstrual age, has multi-factorial causes. Diuretics have been used to prevent or treat established BPD and are the most frequently prescribed medication for the management of severe BPD. There is significant variation in the use of diuretics, and there is limited evidence showing improvement in medium to long term outcomes.

We explored whether the use of diuretics in infants with BPD reduced the duration of HoT in a service that uses a unified protocol-driven pathway to monitor and wean HoT.

MATERIAL AND METHODS: A retrospective cohort study of 281 infants with BPD discharged home with oxygen therapy between 2001 and 2018. Of the 281 infants, 154 had complete data sets and were included in the study population.

RESULTS AND CONCLUSIONS: Forty-nine infants (31.8%) were exposed to at least one diuretic, and 105 infants (68.2%) were not exposed to any. There was no difference in the duration of HoT in infants exposed to diuretics compared to those who were unexposed. Infants exposed to diuretics had a significantly longer length of stay (LoS) in the hospital compared to unexposed infants ($P < .001$). We conclude that in a setting of a service in which diuretics are actively discontinued post-discharge and in which weaning of HoT is driven by a unified protocol, the use of diuretics pre-discharge does not reduce the duration of HoT.

KEYWORDS: Bronchopulmonary dysplasia, diuretics, home oxygen therapy, pediatric lung disease

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common sequelae of preterm birth. An evidence-based approach defines BPD according to the level of respiratory support and supplemental oxygen administered at 36 weeks postmenstrual age.[1] Its causation is multi-factorial with several pre-, peri-, and postnatal factors contributing to its development.[2] Lung edema resulting from fluid overload and lung injury are also contributory.[3] Diuretics act by increasing fluid reabsorption and removing excess lung fluid and blood volume.[3,4] They have been shown to improve lung compliance and reduce airway resistance and ventilatory support in the short term.[3-6] Diuretics are used to remove excess extracellular fluid in infants and are usually initiated when there are cardiovascular concerns (congestive heart failure) or respiratory requirement (BPD infants with severe CXR changes or increased ventilatory requirements). For many years, diuretics have been used to prevent or treat established BPD and are the most frequently prescribed medication for the management of severe BPD;[7] however, there is significant variation in dosage, duration and types of diuretic used[3,4] as well as weaning strategies and the sequence of weaning oxygen versus diuretics.[8] Additionally there is limited evidence showing improvement in medium- to long-term outcomes (mortality, duration of home oxygen therapy (HoT), length of stay in hospital (LoS)) in infants with BPD who were exposed to diuretics.[5,6] Furthermore, clinical benefits of a longer DoDT may not differ much from that of a shorter DoDT.[3] The lack of benefit from sustained use of diuretics may be due to adaptation limits and tolerance to the effect of diuretics as experimental evidence suggests.[9] Additionally, the use of diuretics in infants comes with potential side effects like electrolyte and acid-base imbalances, dehydration, hypovolemia, osteopenia, pre-renal failure, nephrocalcinosis, and endocrine and metabolic effects.[6]

Structured monitoring and weaning pathways for HoT lead to improved outcomes[10,11] including reduction in the duration of HoT, and have been used in our tertiary BPD service for over 16 years.

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This study explores whether the use of diuretics in infants with BPD reduced the duration of HoT in a service that uses a unified protocol-driven pathway to monitor and wean HoT. We also explored whether the use of diuretics reduces LoS on the neonatal unit.

MATERIAL AND METHODS

A retrospective cohort study of 281 infants with BPD discharged home with oxygen therapy between 2001 and 2018 was conducted. Bronchopulmonary dysplasia was defined as the ongoing requirement for oxygen administration after 36 corrected weeks gestation in the absence of an alternate cause. Home oxygen therapy was defined as the requirement to provide oxygen to the infant at the point of discharge. The duration of HoT was obtained from a database that uses a structured monitoring and weaning pathway for HoT. Infants discharged home from the neonatal unit on diuretics had these actively discontinued within 2 weeks of discharge from the hospital.

Clinical data not included in our database were obtained from the Digital Health Record. This included drugs used during neonatal unit admission, the duration of diuretic therapy (DoDT), and LoS. Diuretics that were prescribed to infants included furosemide, spironolactone, hydrochlorothiazide, and chlorothiazide. Demographics and comorbidities that could be associated with diuretic use and length of stay included gender, gestational age, birthweight, and cardiovascular comorbidities (atrial septal defect: ASD, ventricular septal defect: VSD, and patent ductus arteriosus: PDA).

We used the duration of home oxygen therapy as a global indicator of the severity of and recovery from BPD. Initially, we described the demographics of the infants exposed to diuretics versus non-exposed. We compared data on a non-parametric basis with a Wilcoxon test, and categorical data were compared with the prop test (as implemented in R). We plotted the univariate data distributions with histograms, and as they were not clearly normally distributed, we took a cautious approach and used a Wilcoxon test. We undertook a Kaplan–Meier survival analysis with the duration of HoT as the outcome measure and neonatal unit diuretic administration as the predictor, using the log-rank test to compare groups on a univariate basis.

We reasoned that the administration of diuretics in the neonatal unit would improve lung function in BPD, leading to a shorter duration of HoT after discharge. We modeled this with a Cox proportional hazard model, with the duration of HoT as the outcome, administration of diuretics in the neonatal unit as the predictor covariate, and birthweight, gender, gestational age, and cardiovascular comorbidities as covariates. Covariates were chosen a priori as likely to influence the decision to prescribe or not prescribe diuretics. Data were analyzed on a complete cases basis. R (version 4.3.1) was used for statistical analysis, with the packages Survival, ggplot2, and survminer.

Ethical approval was not deemed necessary as the project was registered with the Hospital Clinical Effectiveness Department (Registration ID 24-067C), and the analysis was undertaken as a service evaluation of established practice as per departmental guidelines.

Main Points

- In a setting of a unified, protocol-driven service for babies with BPD, the use of diuretics does not reduce the duration of home oxygen therapy.
- Infants with BPD who were exposed to diuretics had a longer length of hospital stay.
- This study adds to the body of evidence that infants with BPD are exposed to medications of unclear efficacy and safety with regard to medium term outcomes like the duration of home oxygen therapy.

RESULTS

Of the 281 infants, 154 had complete data sets and were included in the study population. Forty-nine infants (31.8%) were exposed to at least one diuretic, and 105 infants (68.2%) were not exposed to any (Figure 1). Two percent of the infants received four different diuretics, 51% received three different diuretics, 30.7% received two different diuretics, and 16.3% received one diuretic. Furosemide and spironolactone were both most commonly prescribed (83.7% each), followed by chlorothiazide (38.8%) and hydrochlorothiazide (34.7%). The exposed infants received a median of 35 days of diuretics (25th-75th percentile: 8-71 days).

The demographic details in the exposed versus not exposed groups were comparable. There was no difference in the duration of HoT in infants exposed to diuretics as compared to those who were unexposed (128 vs. 108 days, $P = .26$). Infants exposed to diuretics had a significantly longer LoS in the hospital compared to unexposed infants (104 vs. 85 days

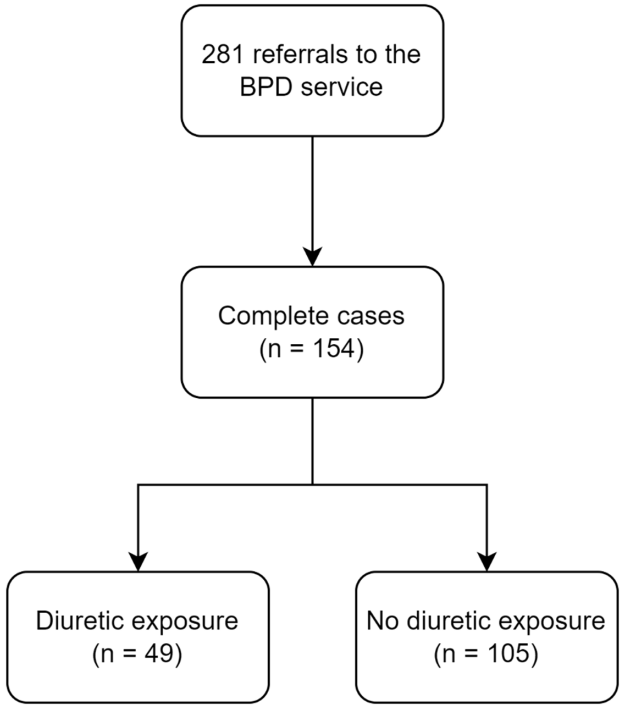

Figure 1. Flow diagram of the patient population.

Table 1. Demographics of the Cohort

	Diuretics	No Diuretics	*P* Value
Number	49	105	
Male sex, n (%)	29 (59.2)	70 (66.7)	.47
Gestational age (weeks + days) median [IQR]	27^{+0} [25^{+0}-29^{+2}]	26^{+3} [25^{+0}-27^{+6}]	.22
Birthweight (g) median [IQR]	880 [740-1200]	830 [680-990]	.06
Diuretic (days) median [IQR]	35 [8-71]	0 [0-0]	NA
Length of NICU stay (days) median [IQR]	104 [87-124]	85 [67-102]	<.001
Duration of home oxygen treatment median [IQR]	128 [87-174]	108 [72-175]	.26
Cardiovascular comorbidity, n (%)	33 (67.3)	43 (41.0)	<.01

Demographics of the study population. Continuous variables were analyzed with Wilcoxon rank-sum test; categorical variables were analyzed with the proportion test. All analyses were undertaken in R.

P < .001; (Table 1). Children on diuretics had a greater length of NICU stay and were more likely to have a cardiovascular comorbidity. For those infants who were discharged home on diuretics, the diuretics were actively discontinued within 2 weeks of discharge from the hospital. Some of the infants who received diuretics in this study had both BPD and cardiovascular comorbidities (and this was accounted for in our statistical analysis).

We undertook a survival analysis initially modeling the duration of HoT, with the binary predictor ever exposed to diuretics, and found no evidence for an association with the duration of HoT (Figure 2; log-rank test *P* = .33). To explore this further, we made a multivariate Cox proportional hazard model of the duration of HoT, with diuretic use as the primary predictor, and gender, gestational age, birthweight, and comorbidities as the covariates. There was no evidence for an association between HoT and diuretic exposure in this model (hazard ratio 0.84, 05% CI 0.59-1.19, *P* = .327; see Table 2 and Figure 3 for a summary of the model).

To further explore the impact of diuretics on the length of stay in the neonatal unit, we investigated the association between diuretic use and length of stay in a Cox proportional hazard model (Table 3). In a model with the same covariates, but with the length of neonatal stay as the outcome, diuretics were associated with a reduced hazard of discharge (i.e., a longer duration of stay) on the neonatal unit after accounting for gender, gestational age at birth, birthweight, and cardiovascular comorbidities (HR 0.36; 95% CI 0.24-0.53, *P* < .001). As would be expected for a model including length of stay, in this model gestational age was significantly associated with length of stay (HR 1.04; CI 1.02-1.05; *P* < .001).

DISCUSSION

In this retrospective analysis, we found that in a setting of a service in which diuretics are actively discontinued post-discharge, and in which weaning of HoT is driven by a unified protocol, the use of diuretics pre-discharge does not reduce the duration of HoT, and those infants exposed to diuretics had a significantly longer LoS compared to unexposed infants.

Our finding is consistent with the findings from a randomized control trial in which Kao et al[12] reported no difference in the total duration of supplemental oxygen use (diuretic group 133 ± 53 days vs. placebo group 147 ± 71 days). A Cochrane systematic review demonstrated that diuretics

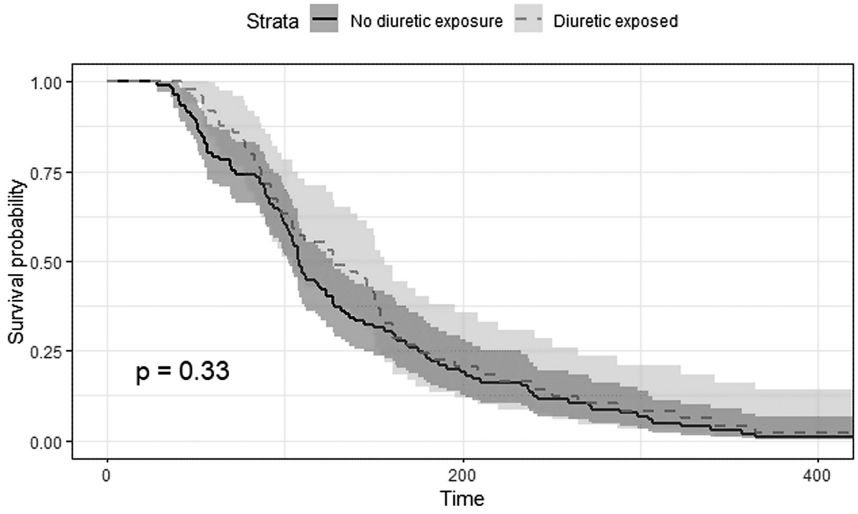

Figure 2. Survival plot for the outcome duration of home oxygen therapy (HoT). Shaded areas indicate 95% confidence intervals. HoT, home oxygen therapy.

Table 2. Cox Proportional Hazard Model for Risk of Cessation of Home Oxygen (i.e., Duration of HoT)

	Hazard Ratio	95% CI	*P*-Value
Ever used diuretics	0.84	(0.59-1.19)	.337
Male gender	1.04	(0.74-1.46)	.83
Gestational age (days)	1.00	(0.99-1.02)	.39
Birthweight (g)	1.00	(0.99-1.00)	.60
CVS comorbidity	1.30	(0.91-1.88)	.15

HoT, home oxygen therapy; CVS, Cardiovascular.

like furosemide, despite improving pulmonary compliance, lead to inconsistent improvement of oxygenation in preterm infants <3 weeks of age developing BPD. In patients >3 weeks of age with BPD, despite transient improvement in pulmonary mechanics and oxygenation, no data was available on total duration of O_2 administration, incidence of BPD, or chronic lung disease at 36 weeks postmenstrual age.[5] With regards to thiazide diuretics, there is no evidence that administration has any impact on duration of O_2 dependency, duration of ventilator dependency, LoS, and long-term outcome in patients exposed to diuretic therapy.[6] In an observational, whole population study, 44.6% of 9457 infants who survived had received diuretics for at least 7 days. In this study, diuretic use did not reduce the need for supplemental oxygen upon discharge home from the neonatal intensive care unit.[13] Our finding that the duration of HoT for those infants who were discharged home on diuretics and had their diuretics actively discontinued within 2 weeks of discharge from the hospital was no different from the unexposed group. This is comparable to Dawson et al,[14] who found no differences in home oxygen duration in infants actively weaned versus not on diuretics but those who were passively weaned had a longer duration of home oxygen.

It is not surprising that diuretics do not lead to sustained or long-term improvements in pulmonary manifestations of BPD, as the major injury drivers for the fetal lung are inflammation and developmental disruptions such as growth restriction and nicotine exposure[15] rather than fluid overload.

We also found that infants exposed to diuretics had a significantly longer LoS compared to unexposed infants (Table 3 and Figure 4). The use of diuretics in infants with BPD could also represent a marker of more severe BPD requiring pharmacological intervention, and there is likely confounding by indication. Infants who were started on diuretics tended to be more ill compared to those who did not receive diuretics and hence it makes sense for them to need a longer period of care in hospital overall. Our findings are similar to the observational cohort study by Blaisdell et al. which demonstrated that infants with BPD exposed to diuretics needed more respiratory support compared to those who were unexposed, and this may reflect that these babies were given more support afterward, whether needed or not. Alternatively, it reflects the recognition of an infant with deteriorating respiratory status who failed to/had a partial response.[4]

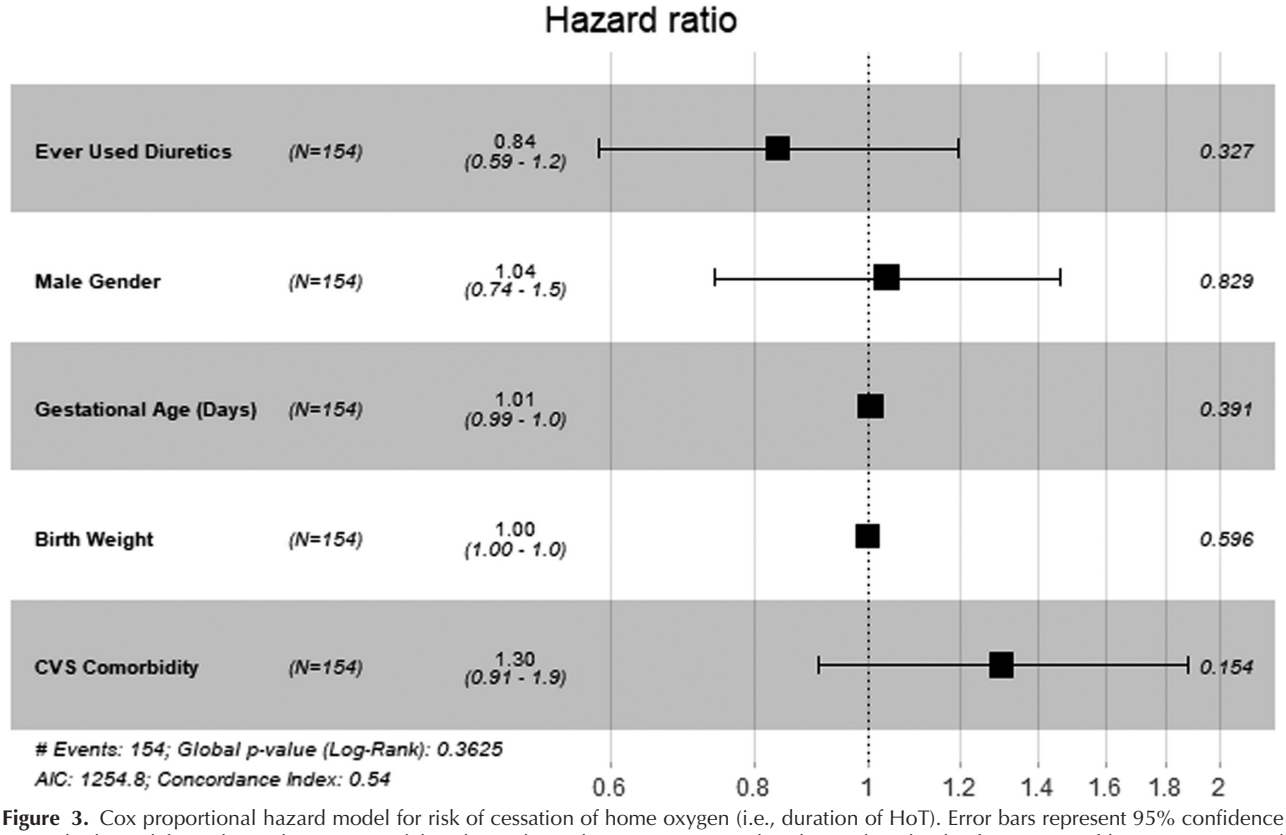

Figure 3. Cox proportional hazard model for risk of cessation of home oxygen (i.e., duration of HoT). Error bars represent 95% confidence intervals derived from the multivariate model. A lower hazard ratio is associated with a reduced risk of cessation of home oxygen (and therefore a longer duration of HoT). HoT, home oxygen therapy.

Table 3. Cox Proportional Hazard Model for Risk of Discharge from the Neonatal Unit (i.e., Duration of Neonatal Length of Stay)

Variable	Hazard Ratio	95% CI	*P*-Value
Ever used diuretics	0.36	(0.24-0.53)	<.001
Male gender	0.94	(0.66-1.35)	.74
Gestational age (days)	1.04	(1.02-1.05)	<.001
Birthweight (g)	1	(0.99-1.00)	.87
CVS comorbidity	1.11	(0.79-1.58)	.57

HoT, home oxygen therapy.

Taken together, our findings confirm the need for clinicians to critically evaluate the response to diuretics in infants with BPD. The ERS taskforce suggests that for those children with BPD who have already received treatment with diuretics from the neonatal phase or neonatal intensive care unit onward, natural weaning occurs by the relative decrease in dose with increasing weight gain. If the treating physician considers the use of diuretics to have additional value, for example, when clinical signs of fluid retention are present, the effects of treatment with diuretics should be carefully monitored during a trial period before being chronically applied.[16]

There are limitations to our study. Firstly, the types of diuretics used were not consistent across the 49 infants. We are thus unable to conclude generally for all types of diuretics. Secondly, the analysis was unable to take into account the impact of other respiratory medications such as bronchodilators or corticosteroids that some of the infants might have been on; however, we believe that the use of a consistent protocol-driven approach to monitoring and weaning HoT applies across the whole cohort to provide robust data for the duration of HoT. Thirdly, given the retrospective nature of our study, both groups of infants are not comparable in terms of the severity of BPD, which was not helped by the small sample size (49) of infants that were exposed to diuretics, even if there was a wide distribution in gestational age and birthweight. Both groups of infants with BPD have had different clinical courses in the neonatal unit, with the group receiving diuretics presumed to be more ill, requiring diuretic intervention. It is surprising to find that there is no difference in HoT between both groups of infants, and this study shows the need for further studies like a randomized controlled trial to evaluate the efficacy of diuretics use in infants with BPD.

CONCLUSION

We conclude that in a setting of a service in which diuretics are actively discontinued post-discharge, and in which weaning of HoT is driven by a unified protocol, the use of diuretics pre-discharge does not reduce the duration of HoT. It is also surprising to find that infants who were exposed to diuretics had a longer LoS, albeit not a longer HoT. This study adds to the body of evidence that infants with BPD are exposed to medications of unclear efficacy and safety with regard to medium-term outcomes like the duration of HoT. Further work in the form of randomized controlled trials of diuretic use versus placebo treatment in infants with BPD will

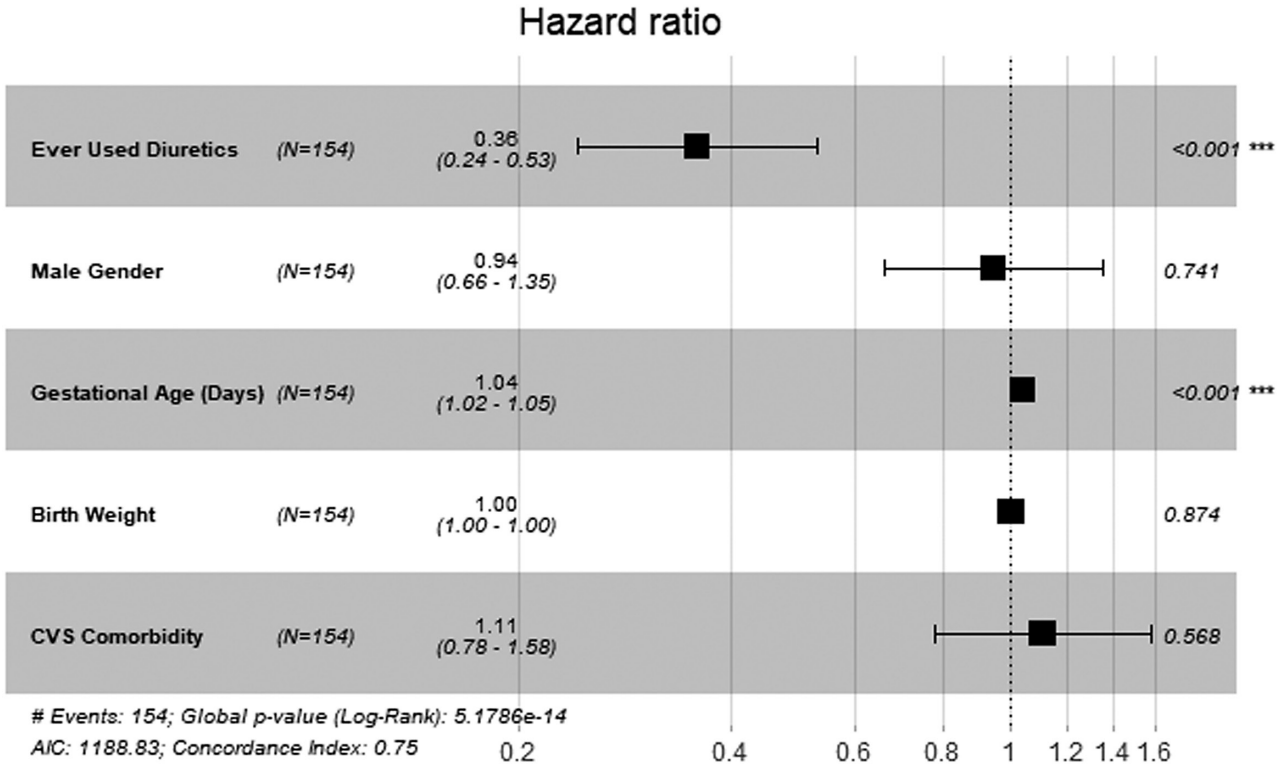

Figure 4. Cox proportional hazard model for risk of discharge from the neonatal unit (i.e., duration of neonatal length of stay). Error bars represent 95% confidence intervals derived from the multivariate model. A lower hazard ratio is associated with a reduced risk of discharge (and therefore a longer neonatal stay).

be needed to corroborate the true efficacy of diuretic use in this group of infants.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical approval was not deemed necessary as the project was registered with Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust Clinical Effectiveness Department (Registration ID 24-067C), and the analysis was undertaken as a service evaluation of established practice as per departmental guidelines.

Informed Consent: Informed Consent was not deemed necessary as the project was registered with Nottingham Children's Hospital, Queen's Medical Centre, Nottingham University Hospitals NHS Trust Clinical Effectiveness Department (Registration ID 24-067C), and the analysis was undertaken as a retrospective service evaluation of established practice as per departmental guidelines.

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Author Contributions: Concept – A.P., D.B., J.M.B.; Design – AP, ycc, DB, JMB Supervision – A.P., D.B., J.M.B.; Resources – A.P., D.B., J.M.B.; Materials – A.P., Y.C.C., D.B., J.M.B.; Data Collection and/or Processing – A.P., Y.C.C., D.B., J.M.B.; Analysis and/or Interpretation – A.P., J,M,B.; Literature Search – A.P., Y.C.C., D.B., J.M.B.; Writing – A.P., Y.C.C., D.B., J.M.B.; Critical Review – A.P., D.B., J.M.B.

Declaration of Interests: The authors have no conflicts of interest to declare.

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