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BREED-SPECIFIC APPROACH OF BIRTH WEIGHT AS A RISK FACTOR FOR NEONATAL MORTALITY IN THE CANINE SPECIES

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SUMMARY

In numerous species, low birth weight has been identified as risk factor for neonatal mortality. In the canine species, suffering from around 15% of postnatal mortality, definition of a low birth weight is made complex by the huge interbreed variability in stature. To define this parameter, data from 6,694 puppies (27 breeds, litters and 75 French breeding kennels) were collected and analysed. A generalized linear mixed model was fitted to identify risk factors for puppy mortality within the first three weeks after birth. Then, receiver operating characteristics analysis was used to define breed-specific thresholds for birth weight to identify puppies at higher risk of postnatal death. Depending on the breed, critical thresholds defined ranged from 100 grams (Chihuahua) to 500 grams (Leonberger and Berner Sennenhund). Our results should help puppy management in order to reduce postnatal mortality and to increase productivity in dog breeding.

INTRODUCTION

Despite progress of veterinary medicine, mortality rate from birth to weaning remains high in the canine species with around 1 puppy out of 5 dying before the age of 2 months (Chastant-Maillard et al., 2017; Gill, 2001; Indrebø et al., 2007). To improve and optimize breeding, increased knowledge regarding factors influencing neonatal and pediatric mortality is essential.

In a lot of species such as humans, pigs or calves, low birth weight is regarded as a major risk factor for neonatal mortality (Fix, 2010; Wu et al., 2006). In dogs, it was demonstrated that underweight puppies have higher risk of death (Groppetti et al., 2015; Mila et al., 2015). However, these studies generally focused on only few breeds or worked at breed size level (Fiszdon and Kowalczyk, 2009; Indrebø et al., 2007; Nielen et al., 2001). Nevertheless, selective breeding of domestic dog (*Canis familiaris*) has produced hundreds of varied breeds showing the greatest morphological variability of any land mammal with a body weight ranging from 500 grams in miniature breeds like Chihuahua to more than 100 kilograms in giant ones (Mastiff) (Boyko et al., 2010). So, breed-specific information on birth weight are necessary.

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The aim of this study was to evaluate the impact of birth weight on neonatal puppy mortality in a large canine purebred population, and to determine breed-specific cut-off values for birth weight.

MATERIALS AND METHODS

Data collection

This study was based on data collected through a questionnaire administered to dog breeders from 2015 to 2017. At the end of the period of data collection, a data selection process was performed in order to include only puppies born in French breeding kennels with birth weight provided and puppies from breeds with at least 100 individuals in the dataset.

Parameters studied

Explanatory variables were selected based on their biological relevance and introduced in the models only if missing values represented less than 15% of the data. Outcomes and explanatory variables considered in the analysis were: neonatal mortality (number of puppies that died during the first three weeks after birth), presence of stillborn in the litter, sex of the puppy, size of breeding kennel (total number of puppies born per year), litter size and birth weight. The size of breeding kennel was categorized into three groups: “Small” for breeding kennels producing less than 10 puppies per year; “Medium” for 10 to 50 puppies per year and “Large” with more than 50 puppies per year.

Statistical analyses

Statistical analyses were performed using R software (R Core Team, 2016) (version 3.3.2) with add-on packages “lme4” (Bates et al., 2015) and “pROC” (Robin et al., 2011). Results with p-values < 0.05 were considered to be significant and statistical uncertainty was assessed by calculating exact 95% binomial confidence intervals (95% CI).

A generalized linear mixed model was fitted, where outcome variable was neonatal mortality (0/1). The fixed-effects introduced in the model were birth weight, presence of stillborn in the litter, sex, litter size and breeding kennel size. Significant interactions existed between breed and litter size and birth weight ($p < 0.001$, Kruskal-Wallis rank sum test). So, breed effect was introduced by classifying these two parameters using breed-specific quartiles. Litter size was categorized into three groups (1: < Quartile 1 (Q1); 2: [Q1-Q3]; 3: \geq Q3) with quartile values calculated at litter level. Birth weight was categorized into four groups thanks to quartiles calculated at puppy level (1: < Q1; 2: [Q1-Q2]; 3: [Q2-Q3]; 4: \geq Q3). Breeding kennel and dam were introduced as random effects to deal with the non-independence of puppies sharing the same breeding kennel and the same mother.

To deal with our imbalanced data, we applied the random under sampling approach described by Chan and Stolfo (Chan and Stolfo, 2001; Weiss, 2004) and generalized linear mixed model was fitted with all selected variables and validated for each sub-datasets using holdout method. Results were combined across balanced sub-datasets using the median. Thus, p-values, odds ratio and their 95% CI were obtained for each parameters. Moreover, the median area under the receiver operating characteristic curve (AUROC) was used to assess the ability

of the model to differentiate between puppies which die during neonatal period and those which do not.

In a second step, ROC curves were used to identify optimal cut-off values for birth weight. The effectiveness of the parameter to discriminate between puppies dying before three weeks of age and the ones which are still alive at the end of neonatal period was assessed using the AUROC. For each breed, if the AUROC was greater than or equal to 0.70, cut-off value was determined and was the one which maximized Youden's J statistic ($J = Se + Sp - 1$) with a sensitivity greater than or equal to 75% in order to minimize false negative rate (Greiner et al., 2000; Hajian-Tilaki, 2013).

RESULTS

Study population

A total of 6,694 live-born puppies from 27 breeds, 1,202 litters and 75 French breeding kennels were included. Litters were born between 1994 and 2017 with 82% of the litters born over the last 10 years (from 2007 to 2017). Twelve of the twenty most represented breeds in France according to the LOF (Société Centrale Canine, 2018) (Livre des Origines Françaises – French Association recognized by the government to manage pedigree dogs) were included in this study. Median number of puppies included per breed was 155, ranging from 104 to 1,846 puppies. The global mean litter size at birth was 6.3 (± 2.7) puppies and the sex ratio was 1 (3,313 males and 3,314 females). Average birth weight ranged from 119.6 (± 25.6) g for Chihuahua to 630.3 (± 112.1) g for Newfoundland.

Puppy mortality risk factors

A total of 9% (604/6,694; 95%CI: 8.3-9.7) of live-born puppies died during their first three weeks of life (Table 1). Neonatal mortality was influenced by birth weight ($P < 0.001$) and size of breeding kennel ($P = 0.014$) (Table 1). Mortality during the first three weeks of life was significantly higher in puppies with birth weight lower than the first quartile than the others: 17.8% (95%CI: 16 – 19.7) vs. 8.5% (95%CI: 7.2 – 9.9), 5.5% (95%CI: 4.4 – 6.7) and 3.7% (95%CI: 2.8 – 4.8) for respectively groups 2, 3 and 4 of birth weight. Moreover, neonatal mortality was significantly higher in large and small breeding kennels (mortality rate at 10.8% (95%CI: 9.9 – 11.7) and 5% (95%CI: 3.9 – 6.4) respectively) than in medium breeding kennels with a mortality rate of 2.3% (95%CI: 1.1 – 4.1). Finally, puppies with birth weight lower than the first quartile born in large breeding kennel were more at risk of neonatal death compared to puppies from other categories: mortality rate respectively at 20.7% (95%CI: 18.5 – 23) and 6.3% (95%CI: 5.6 – 7) (Fig. 1). Model studied presented a good discrimination power with a median AUROC of 0.80 (range: 0.77 – 0.83).

Table 1. Potential risk factors associated with neonatal puppy mortality

Risk factor	P-value	Odds ratio (95% CI)
Size of breeding kennel	0.014	
Small		1 (Ref.)
Medium		0.18 (0.03-1.08)
Large		2.25 (0.78-7.35)
Presence of stillborn in the litter	0.407	
No		1 (Ref.)
Yes		0.84 (0.52-1.35)
Litter size	0.479	
Small		1 (Ref.)
Medium		1.05 (0.64-1.72)
Large		1.47 (0.66-3.27)
Birth weight	<0.001	
Q1		1 (Ref.)
Q2		0.34 (0.2-0.56)
Q3		0.18 (0.1-0.33)
Q4		0.08 (0.04-0.17)
Sex	0.225	
Female		1 (Ref.)
Male		1.29 (0.86-1.93)

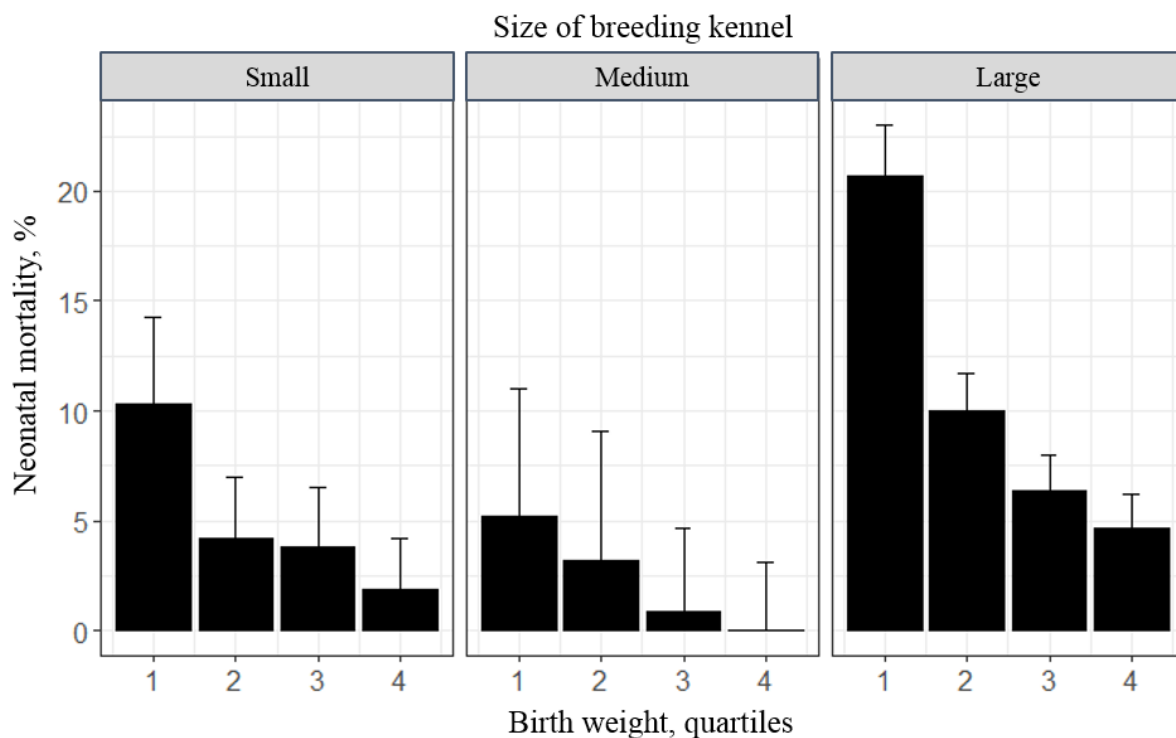


Fig. 1 Neonatal mortality (during the first three weeks of life) according to birth weight and size of breeding kennel

Birth weight cut-off determination

Birth weight cut-off regarding neonatal mortality have been identified for 12 breeds with Area Under the Receiver Operating Characteristics Curve (AUROC) greater than or equal to 0.70 (Table 2). For all the breeds, birth weight cut-off was higher than first quartile.

Table 2. Breed-specific cut-off values for birth weight identified using receiver operating characteristics (ROC) analysis

Breeds	AUROC (95% CI) ^a	BW cut-off value, grams (SE;SP) ^b
Australian Shepherd Dog	0.72 (0.58-0.85)	375 (75;45)
Berner Sennenhund	0.75 (0.65-0.84)	480 (100;50)
Cocker Spaniel	0.73 (0.65-0.81)	280 (84;45)
French Bulldog	0.71 (0.57-0.85)	230 (82;60)
German Shepherd Dog	0.75 (0.62-0.88)	480 (75;59)
Jack Russel Terrier	0.71 (0.54-0.88)	202 (83;59)
Labrador Retriever	0.75 (0.70-0.79)	406 (77;56)
Leonberger	0.75 (0.65-0.85)	480 (77;68)
Lhasa Apso	0.81 (0.7-0.91)	184 (84;60)
Maltese	0.76 (0.64-0.88)	162 (75;57)
Rottweiler	0.7 (0.58-0.83)	410 (81-52)

West Highland White Terrier 0.7 (0.58-0.82) 209 (85;41)

^a Area Under the Receiver Operating Characteristics Curve with 95% confidence interval

^b Birth weight cut-off with sensitivity and specificity

DISCUSSION

In the present study, including 6,694 puppies from 27 breeds represented by at least 100 puppies, neonatal mortality rate was 9% and was in the range of postnatal mortalities previously reported. In the study of Chastant-Maillard et al. (2017) on a large French population including 248 breeds with 204 537 puppies, postnatal mortality was 6.5%, and Indrebø et al. (2007) found that 7.5% of live born puppies died during the first 8 weeks (n=744). In the study of Gill (2001), 13.2% of the puppies that were born alive, died during the first 6 weeks (n=2,574).

Average birth weight varied from 119.6 to 630.3 grams depending on breed considered, which is closed compared to previous studies (Bigliardi et al., 2013; Gill, 2001; Groppetti et al., 2017; Trangerud et al., 2007). As already noted, birth weight was significantly influenced by breed (Čechová, 2006; Chatdarong et al., 2007; Fiszdon and Kowalczyk, 2009; Groppetti et al., 2017). For example, German Shepherd Dog, Golden Retriever, Labrador Retriever and Boxer adult weights range from about 25 to 30 kilograms (Hawthorne et al., 2004; Helmink et al., 2000; Posada et al., 2014; Trangerud et al., 2007) and their average birth weight were different (respectively 506, 396, 410 and 464 grams). This highlights the importance of breed-specific studies on canine birth weight and growth. Average birth weight of breeds of identical adult weights range

In our study, low birth weight puppies presented a significantly higher risk of death compared to normal birth weight puppies (mortality rate 3 times higher in low birth weight). This impact of birth weight was already described as a major determinant for puppy survival (Lawler, 2008; Mila et al., 2015). Various factors, like an increased risk of hypoglycemia and hypothermia, could explain the higher losses in low birth weight puppies (Münnich and Küchenmeister, 2014). So, low birth weight puppies will require appropriate nursing and medical care to improve their chances of survival. Nevertheless, studies defined arbitrarily low birth weight puppies as a puppies belonging to the 25 % lighter animals (Mila et al., 2015). In our study, we used ROC analysis, for each breed, to define objectively a low birth weight. Specific thresholds were defined for 12 breeds and 48% of the puppies were to be considered at risk for neonatal mortality (2,026 puppies on 4,260 had birth weight lower than the cut-off). These results suggest that, puppies susceptible to neonatal death are not only the ones which are more than 25% below the average birth weight as previously reported (Mila et al., 2015; Münnich and Küchenmeister, 2014).

Neonatal mortality was also significantly different depending on the size of the breeding kennel. Breeding kennels selling more than 50 puppies per year faced to the highest mortality rate. Moreover, mortality rate was higher in breeding kennels selling 10 to 50 puppies per year than in the ones selling less than 10 puppies per year. The higher losses in large breeding kennels could be explained by their increased susceptibility to infectious diseases. Indeed, a significantly higher prevalence of enteropathogens was described in large breeding kennels (i.e. selling more than 30 puppies per year) (Grellet et al., 2014). Moreover, breeding kennel with less than 10 puppies per year should be amateur breeders potentially with a less technical approach.

To conclude, evaluation of weigh at birth is an easy-to-use tool for early identification of newborn dogs at higher risk of neonatal mortality. Critical thresholds presented in this study would allow to identify puppies with low birth weight and to provide them an appropriate nursing and medical care. Further investigations are warranted to define birth weight thresholds for the numerous remaining canine breeds. Moreover, due to a possible ‘bloodline effect’, birth weight on a same breed across different countries have to be studied.

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