Short communication: Prediction of hyperketonemia in dairy cows in early lactation using on-farm cow data and net energy intake by partial least square discriminant analysis

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ABSTRACT

The objectives of this study were (1) to evaluate if hyperketonemia in dairy cows (defined as plasma β -hydroxybutyrate ≥ 1.0 mmol/L) can be predicted using on-farm cow data either in current or previous lactation week, and (2) to study if adding individual net energy intake (NEI) can improve the predictive ability of the model. Plasma β -hydroxybutyrate concentration, on-farm cow data (milk yield, percentage of fat, protein and lactose, fat- and protein-corrected milk yield, body weight, body weight change, dry period length, parity, and somatic cell count), and NEI of 424 individual cows were available weekly through lactation wk 1 to 5 postpartum. To predict hyperketonemia in dairy cows, models were first trained by partial least square discriminant analysis, using on-farm cow data in the same or previous lactation week. Second, NEI was included in models to evaluate the improvement of the predictability of the models. Through leave-one trial-out cross-validation, models were evaluated by accuracy (the ratio of the sum of true positive and true negative), sensitivity (68.2% to 84.9%), specificity (61.5% to 98.7%), positive predictive value (57.7% to 98.7%), and negative predictive value (66.2% to 86.1%) to predict hyperketonemia of dairy cows. Through lactation wk 1 to 5, the accuracy to predict hyperketonemia using data in the same week was 64.4% to 85.5% (on-farm cow data only), 66.1% to 87.0% (model including NEI), and using data in the previous week was 58.5% to 82.0% (on-farm cow data only), 59.7% to 85.1% (model including NEI). An improvement of the accuracy of the model due to including NEI ranged among lactation weeks from 1.0% to 4.4% when using data in the same

lactation week and 0.2% to 6.6% when using data in the previous lactation week. In conclusion, trained models via partial least square discriminant analysis have potential to predict hyperketonemia in dairy cows not only using data in the current lactation week, but also using data in the previous lactation week. Net energy intake can improve the accuracy of the model, but only to a limited extent. Besides NEI, body weight, body weight change, milk fat, and protein content were important variables to predict hyperketonemia, but their rank of importance differed across lactation weeks.

Key words: partial least square discriminant analysis, metabolic status, subclinical ketosis

Short Communication

In early lactation, dairy cows typically have a negative energy balance, which has been related to metabolic disorders such as hyperketonemia (Grummer, 1993; Duffield et al., 2009). Hyperketonemia is defined as an increased concentration of plasma BHB. Commonly used thresholds for hyperketonemia are plasma concentration of BHB ≥ 1.0 to ≥ 1.4 mmol/L in dairy cows (Walsh et al., 2007; Duffield et al., 2009). The incidence of hyperketonemia is especially high (up to 45.7%) in the first weeks after calving (McArt et al., 2013). Hyperketonemia is related to an increased risk of disorders in peripartum period, such as subclinical and clinical ketosis (Geishauser et al., 2000; Duffield et al., 2009), left-displaced abomasum (Geishauser et al., 1997), and decreased reproductive performance (Walsh et al., 2007). An annual loss for subclinical ketosis, clinical ketosis, left-displaced abomasum, and decreased reproductive performance ranges from £50 to £280 per cow (Kossaibati and Esslemont, 1997). Reliable assessment of hyperketonemia could thus diagnose cows that are prone to metabolic disorders, but without clinical signs yet. Urine or milk ketone tests have been applied

Received July 18, 2019.

Accepted March 16, 2020.

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as cow-side tests to diagnose hyperketonemia in dairy cows on farms (Nielen et al., 1994). In addition, plasma BHB has been estimated using milk fat-to-protein ratio (Duffield et al., 1997), milk metabolites (Klein et al., 2012), and Fourier-transform infrared spectroscopy based on milk samples (van Kneegsel et al., 2010; Bonfatti et al., 2019; Luke et al., 2019; Renaud et al., 2019). Alternatively, increasing number of variables are available on-farm and can be hypothesized of value to estimate hyperketonemia in dairy cows. In addition, mostly plasma BHB was estimated using data in the same lactation week, however, not using data from previous lactation week. To our knowledge, only Ehret et al. (2015) predicted milk BHB based on data in the previous lactation week, using milk production traits, and genomic and metabolic information. A reliable and early prediction of hyperketonemia in cows could assist in cow management and potentially reduce the risk for clinical and subclinical metabolic disorders. It could be expected that the prediction of hyperketonemia in cows using data in the previous lactation week will have a lower performance than using data in the same lactation week (Ehret et al., 2015).

In dairy cows, partial least square discriminant analysis (**PLS-DA**) has been used to analyze data with highly-correlated variables, such as metabolomics data (Sun et al., 2014; Kenéz et al., 2016) and Fourier-transform infrared spectroscopy (Valenti et al., 2013; Grelet et al., 2019). It can be hypothesized that hyperketonemia could also be predicted with PLS-DA using on-farm cow data. In fact, it is known that several on-farm cow data, such as milk yield (Lean et al., 1992), milk fat and protein percent (Duffield et al., 1997), and BW (Bernabucci et al., 2005) are related to plasma BHB, or risk for clinical and subclinical ketosis. Moreover, the number of commercial farms collecting information on net energy intake (**NEI**) of individual cows is slowly increasing, which would facilitate inclusion of NEI in the on-farm cow data set to predict hyperketonemia. The correlation among different on-farm cow variables, such as milk yield, milk fat, and protein, results in intricate dependencies among explanatory variables when used together in the same model (Wilmink, 1987; Xu et al., 2018). Further, it is difficult to find a specific parametric function (e.g., linear, quadratic, and so on) with conventional statistic methods. In this context, PLS model have been introduced to deal with data sets with a high degree of among correlation among predictor variables, situations where classical models fail (Wold et al., 2001). We hypothesize that hyperketonemia in dairy cows can be predicted using on-farm cow data and NEI in early lactation using PLS-DA. Objectives of this study were (1) to evaluate if hyperketonemia in dairy cows can be predicted using on-farm cow data

either in the same or previous lactation week, and (2) to study if adding individual NEI can improve the predictive ability of the model.

The concentration of plasma BHB, on-farm cow data, and NEI of 424 cows originate from study I (van Kneegsel et al., 2007), study II (van Kneegsel et al., 2014; Chen et al., 2016), and study III (van Hoeij et al., 2017). In study II, data were collected from the same dairy cows during 2 consecutive lactations, first lactation was reported by van Kneegsel et al. (2014), and second lactation was reported by Chen et al. (2016). Experimental protocols were approved by the Institutional Animal Care and Use Committee of Wageningen University. Briefly, plasma and milk samples were collected weekly. The concentration of plasma BHB was measured with kit no. RB1007 (Randox Laboratories, Ibach, Switzerland), as previously described by Graber et al. (2012). On-farm cow data included dry period length (d); parity; BW (kg); weekly BW change (kg/wk, BW in current week minus BW in the previous week); milk yield (kg/d); the percentage of fat, protein, and lactose; fat- and protein-corrected milk production (kg/d); and SCC (cells/mL). Net energy intake (kJ/kg^{0.75}) was calculated by dietary net energy concentration and feed intake of individual cows. Of all 424 individual cows, the number of cows with complete records in each lactation week is presented in Table 1.

In the current study, due to the better metabolic status of dairy cows with shortened or omitted dry period (Chen et al., 2016), a relatively low threshold (BHB $\geq$ 1.0 mmol/L) was used to define hyperketonemia. Hyperketonemia in dairy cows was predicted by PLS-DA using on-farm cow data and NEI. Briefly, on-farm cow data and on-farm cow data combined with NEI, either in the same lactation week or in the previous lactation week, were used as predictor variables (*X* matrix), whereas if dairy cows had hyperketonemia [defined as plasma BHB $\geq$ 1.0 mmol/L (Whitaker et al., 1983; Seifi et al., 2011)] was used, or not, as the target variable in classification (*Y*). Predictor variables in training and testing data set were centered and scaled to unit variance after split in leave-one trial-out cross-validation, which used 2 of 3 studies as the training data set and the remaining study as the testing data set. A large proportion of the cows had a plasma BHB $<$ 1.0 mmol/L (81.4% to 84.5% among lactation weeks), which would give too much weight to cows without hyperketonemia when training models, and would impair the accuracy when predicting hyperketonemia in dairy cows. Therefore, data were re-sampled to obtain a reduced and balanced data set (Grelet et al., 2016). Cows without hyperketonemia were randomly sampled to obtain a data set where the proportion of cows without hyperketonemia was the same as the proportion

of cows with hyperketonemia. In addition, to avoid an overoptimistic accuracy caused by repeated use of the same cow (Wang and Bovenhuis, 2019) in different studies, cows were only present once either in the training data set, or in the testing data set, within the same week. After 5,000 times cross-validation, the predictive ability of models was evaluated by the accuracy (the ratio of the sum of true positive and true negative), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). In the PLS-DA model, variable importance in projection (VIP) score was used to quantify the contribution of each variable (Wold et al., 2001). Data pre-processing, including log-transformation and scaling, model training with PLS-DA, and the component number in PLS-DA (determined by maximum accuracy) were programmed in Python (version 3.6) using modules “pandas,” “numpy,” and “sklearn.” Figures were plotted in R (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria) with package “ggplot2.”

From lactation wk 1 to 5, averaged milk production (SD in parentheses) was 25.5 (8.9), 33.4 (7.7), 37.2 (7.9), 39.2 (8.3), and 39.2 (8.3) kg/d, respectively. Plasma BHB concentration (SD) was 0.70 (0.30), 0.83 (0.62), 0.84 (0.54), 0.84 (0.71), and 0.84 (0.72) mmol/L for lactation wk 1 to 5, respectively. Incidence of hyperketonemia was 12.4%, 20.7%, 20.5%, 17.4%, and 15.8% for lactation wk 1 to 5, respectively.

When applying on-farm cow data in the same week to predict hyperketonemia in cows, the model predicted hyperketonemia best in wk 3 (maximum accuracy $85.5 \pm 5.8\%$), followed by wk 2 ($82.0 \pm 5.5\%$), wk 4 ($81.6 \pm 6.2\%$), wk 5 ($79.5 \pm 7.5\%$), and wk 1 ($79.4 \pm 9.1\%$; Figure 1A). Through lactation wk 1 to 5, sensitivity ranged from 68.2% to 84.9%, specificity from 61.5% to 98.7%, PPV from 57.7% to 98.7%, and NPV from 66.2% to 86.1% (Supplemental Table S1; <https://doi.org/10.3168/jds.2019-17284>).

When applying on-farm cow data in the previous week to predict hyperketonemia in cows, the model predicted hyperketonemia best in wk 4 (maximum accuracy $82.0 \pm 6.3\%$), followed by wk 3 ($81.4 \pm 5.8\%$), wk 5 ($80.4 \pm 6.9\%$), and wk 2 ($65.1 \pm 7.7\%$; Figure 1B). Through lactation wk 2 to 5, sensitivity ranged from 56.3% to 82.8%, specificity from 51.4% to 89.4%, PPV from 51.1% to 90.5%, and NPV from 54.2% to 84.5% (Supplemental Table S1; <https://doi.org/10.3168/jds.2019-17284>).

The ability of model to predict hyperketonemia in dairy cows differed across lactation weeks. Models usually have a better performance to predict cows in study III than cows in study I and II. Prediction of hyperketonemia in dairy cows in wk 3 is better than the prediction in other weeks, independent if data in the same or previous lactation week are used. Dairy cows usually have a greater incidence of hyperketonemia in lactation wk 2 and 3 (Geishauser et al., 2000) in early lactation. In our results, the incidence of hyperketonemia in lactation wk 2 (20.5%) and 3 (20.7%) is greater than the incidence in wk 1, 4, and 5 (range 12.4% to 17.4%). The high incidence of hyperketonemia in wk 3, compared with other weeks, indicates dairy cows are prone to hyperketonemia, which could be related to the maximum accuracy (85.5%) to predict hyperketonemia in wk 3 compared with other weeks. The prediction using data in lactation wk 1, however, was worse than in other weeks, which could be related to the high variation of variables related to milk production at start of lactation (Drackley, 1999). Generally, the prediction of hyperketonemia in dairy cows was better using data in the same week than data in the previous week. In principle, it seems logical that on-farm cow data in the same week give a more accurate prediction because these data reflect the altered metabolic status of a cow real-time. Nevertheless, although metabolic status of cows vary highly across consecutive weeks during

Table 1. Number of cows with complete records (on-farm cow data and individual net energy intake) in lactation wk 1 to 5 in the prediction of hyperketonemia using data in the same (wk n to wk n) and previous (wk n to wk n+1) lactation week¹

Study ²	Completed records in each lactation week				
	wk 1 to wk 1/2 ³	wk 2 to wk 2/3	wk 3 to wk 3/4	wk 4 to wk 4/5	wk 5 to wk 5
Study I	69(93)/69(93)	72(97)/72(97)	72(97)/72(97)	72(97)/71(96)	72(97)
Study II	114(50)/119(52)	114(50)/115(50)	164(72)/164(72)	168(74)/72(56)	168(74)
Study III	91(75)/111(91)	111(91)/111(91)	121(99)/121(99)	121(99)/120(99)	121(99)
Total	274(65)/299(71)	297(70)/298(71)	357(84)/357(84)	361(85)/354(83)	361(85)

¹The hyperketonemia in dairy cows in lactation wk 1 was not predicted by data in the previous week.

²The experimental design, dry period length, and diet in study I were described by van Knegsel et al. (2007), in study II were described by van Knegsel et al. (2014) and Chen et al. (2016), and in study III were described by van Hoeij et al. (2017).

³“Wk n to wk n/n+1” represents number of cows used to predict hyperketonemia in dairy cows in wk n using data in the same week (wk n to wk n) or in the previous week (wk n to wk n+1). “69(93)/69(93)” indicates that the on-farm cow data of 69 (93% in records of study I) cows are used to predict hyperketonemia in lactation wk 1, and 69 (93% in records of study I) cows are used to predict hyperketonemia in lactation wk 2.

Figure 1. Accuracy of partial least squares discriminant analysis to predict hyperketonemia in dairy cows using on-farm cow data (FD; solid line) and using FD combined with net energy intake (NEI; dotted line) either in the same lactation week (A) or in the previous lactation week (B). Error bars represent SD of accuracy.

the first weeks of lactation (Oikonomou et al., 2008), predictive performance based on data in the previous week is reasonably good, compared with data in the same week.

When adding NEI in the same week to predict hyperketonemia in cows in lactation wk 1 to 5, model accuracy improved ($P < 0.05$) with maximum 4.4%, 2.5%, 2.0%, 1.7%, and 1.0%, respectively. When adding NEI in the previous week to predict hyperketonemia in cows in lactation wk 2 to 5, model accuracy improved

($P < 0.05$) with maximum 6.6%, 2.3%, 3.2%, and 1.8%, respectively.

Due to the higher performance of using study III as testing data set, the VIP scores of PLS-DA models to predict hyperketonemia of cows in study III are presented in Figure 2. The VIP scores of PLS-DA models to predict hyperketonemia of cows in study I and study II are presented in Supplemental Figure S1 (<https://doi.org/10.3168/jds.2019-17284>). Results indicate the contribution of each variable to predict hyperketonemia

with and without NEI. Generally, across lactation wk 1 until 5, BW, BW change, milk fat and protein yield, and milk fat and protein percentage are among the best variables to predict hyperketonemia. When NEI was added to the models to predict hyperketonemia, NEI had the relative high contribution among all variables to contribute to the prediction of hyperketonemia, although the increase in model accuracy was limited. Moreover, BW (Halachmi et al., 2004), BW change (Staples et al., 1990), and milk fat and protein yield or percentage (Hurtaud et al., 2000) are all related to NEI in dairy cows. This implies that part of the effect of NEI was already accounted for in the model using on-farm cow data only and explains possibly why the rela-

tive increase in accuracy when adding NEI is marginal. Further study could consider the variance of important variables not only to predict hyperketonemia, but also to predict reproductive performance (Hempstalk et al., 2015), mastitis (Sun et al., 2010), and milk yield (Gianola et al., 2011) with machine learning techniques in the context of precision dairy farming.

In this study, hyperketonemia in dairy cows was predicted using on-farm cow data and on-farm cow data combined with NEI in early lactation by PLS-DA. Although only PLS-DA had been applied in our study, it does not mean PLS-DA is the best algorithm in practice. To find out the best method for predicting hyperketonemia of dairy cows, more advanced

Figure 2. The variable importance in projection (VIP) scores (x-axis) in the first principal component calculated by partial least squares discriminant analysis to predict hyperketonemia in dairy cows in study III with on-farm cow data (FD) only and FD combined with net energy intake (NEI). The x label in each subplot follows the format “wk *n* to wk *m* (FD or FD + NEI),” which is presented as “data of week *n* (wk *n*) to predict hyperketonemia in dairy cows in week *m* (wk *m*).” FPCM = fat- and protein-corrected milk production; Δ BW = BW change; DPL = dry period length; Milk = milk yield.

algorithms could be evaluated, such as random forest, artificial neural networks, and support vector machine. In our previous study, random forest outperformed the other tested algorithms, including artificial neural networks and support vector machine, to predict metabolic status of dairy cows in early lactation (Xu et al., 2019). The accuracy of random forest, artificial neural networks, and support vector machine to predict hyperketonemia, however, was marginally lower than PLS-DA in our preliminary study (Supplemental Table S2; <https://doi.org/10.3168/jds.2019-17284>). Algorithms including random forest and PLS-DA also have been applied in other studies of dairy cows to predict milk yield (Gianola et al., 2011), reproductive performance (Hempstalk et al., 2015), and metabolic status (Xu et al., 2019).

Due to the low incidence of dairy cows with hyperketonemia (12.4%–20.7% through lactation wk 1 to 5), different strategies were considered to improve the model performance (Aiken et al., 2019), as presented in Supplemental Table S3 (<https://doi.org/10.3168/jds.2019-17284>). Models using a data set without sampling and using a data set sampled with two-thirds of cows without hyperketonemia generally had greater accuracy than model using a data set sampled with one-half of cows without hyperketonemia. The marginal difference of sensitivity, specificity, PPV, and NPV among these 3 strategies indicated that an balanced or unbalanced data set did not compromise these values. Therefore, we would suggest to use a balanced data set (50% vs. 50%) to maximize the accuracy range (50%–100%) of a model trained with different data or algorithms.

In conclusion, hyperketonemia in dairy cows can be predicted using on-farm cow data in both the same and previous lactation week, although with some reduction in accuracy when using data in the previous lactation week. Adding individual NEI improved the predictive ability of model with extra 0.2% to 6.6% accuracy. Besides NEI, BW, BW change, milk fat, and milk protein play important roles to predict hyperketonemia in dairy cows.

ACKNOWLEDGMENTS

The authors thank the China Scholarship Council (Beijing, China) for financial support of the PhD study of the first author. The authors thank the staff of Dairy Campus (Lelystad, the Netherlands) and Schothorst Feed Research dairy herd (Lelystad, the Netherlands), Renny van Hoeij (Wageningen University and Research, Wageningen, the Netherlands), and Gerrit Remmelink (Wageningen Livestock Research, Wageningen, the Netherlands) for their assistance during the experiments. The authors have no conflicts of interest.

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