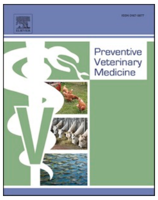
Preventive Veterinary Medicine 241 (2025) 106557

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed



A nutritional prognostic model for hospitalized Belgian blue calves: The Calf-CONUT ratio for predicting survival

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ARTICLE INFO

Keywords:
Urea
Cholesterol
Albumin
Cattle
Nutrition assessment
Prognosis

ABSTRACT

Malnutrition is a major factor in disease management failure. In humans, the CONUT (COntrolling NUTritional status) score assesses nutritional status based on albumin, cholesterol, and lymphocyte levels (sensitivity 92,30 %; specificity of 85 %). In bovine medicine, few studies focus on calf nutrition status. This study compares serum urea, cholesterol, and albumin levels in Belgian Blue calves between hospital admission and discharge (or death) and between survivors (S) and non-survivors (NS). At admission, cholesterol levels did not significantly differ between groups ($p > 0.1$). Albumin levels were higher in S ($p = 0.02$), while urea levels were lower ($p = 0.04$). At discharge, S showed a significant increase in cholesterol ($p < 0.05$) and a decrease in urea ($p < 0.01$) and albumin ($p < 0.05$). A urea/albumin ratio, named the Calf-CONUT ratio, above 2.64 was associated with increased mortality risk (Relative Risk: 2.29, Odds Ratio: 5.75) but demonstrated low sensitivity (46 %) and high specificity (87 %), suggesting limited standalone predictive power. If the analysis focuses solely on calves suffering from enteritis, the threshold value is 2.85, with improved sensitivity and specificity (Se 83 %; Sp 78 %; relative risk: 10; odd ratio: 15). This study provides initial insights into the nutritional assessment of hospitalized calves and paves the way for innovative approaches to their nutritional and medical management. Further research on specific diseases and breeds is needed to refine these thresholds.

1. Introduction

Malnutrition or undernourishment is a major factor in the failure of disease management in human medicine. It is estimated that humans are undernourished at 30–40 % during hospitalization (Ignacio de Ulibarri et al., 2005). Severe malnutrition is estimated at 10 % of the hospitalized population, while nutrition services are consulted only for 3.14 % of patients enduring malnutrition issues (Ignacio de Ulibarri et al., 2005). As a result, human medicine has developed a method for monitoring and assessing patients' nutritional status, named CONUT (COntrolling NUTritional status) score. This score is based on the concentration of albumin, cholesterol and lymphocytes in the blood to detect patients going through malnutrition with sensitivity of 92,30 % and specificity of 85 % (Ignacio de Ulibarri et al., 2005).

In bovine medicine, there is limited literature on calf nutritional status and its impact on treatments' prognosis. Correlations between parameters like blood lactate, arterial blood pressure, shock index (Casalta et al., 2024; Homerosky et al., 2017; Pas et al., 2024; Yildiz et al., 2017) and prognosis were studied in cattle. However, these parameters are valuable for emergency medicine cases like digestive obstruction (Casalta et al., 2024; Trefz et al., 2023). While previous studies (Trefz et al., 2023; Yanar et al., 2023) have examined the role of albumin and urea in critically ill calves, this study is unique in developing a predictive ratio to assess prognosis in a large cohort of hospitalized Belgian Blue calves.

The current research explored 3 nutritional parameters: urea, cholesterol and albumin. Urea is the end product of the amino acid catabolism and the liver's detoxification form of ammonia absorbed by

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https://doi.org/10.1016/j.prevetmed.2025.106557
Received 7 February 2025; Received in revised form 7 April 2025; Accepted 5 May 2025

the digestive tract (Berends et al., 2014). Ruminants are able to recycle urea using rumen micro-organisms to produce more protein, increasing the protein content of their diet. The protein composition of milk is higher than that of solid feed, allowing the calves to meet their significant protein needs, since they are not able to recycle urea (Berends et al., 2014). Blood urea concentration will peak 2–5 days after prolonged starvation in humans (early gluconeogenic phase) and continue to be high for up to ten days (late gluconeogenic phase). After 10 days, urea will decrease during the protein conservation phase and the end of gluconeogenesis (Palmer and Clegg, 2021).

Cholesterol is one of the biochemical parameters that can be measured to assess the energy aspect of the nutritional status of a preruminant calf. Cholesterol concentration rises when there is a high source of unsaturated fatty acids in the diet and falls when lipid reserves are depleted (severe protein-calorie malnutrition) (Hocquette and Bauchart, 1999). In human medicine, this parameter is part of the CONUT as a marker of caloric depletion (Ignacio de Ulibarri et al., 2005). However, it is noteworthy that high-density lipoproteins (HDL), which transport the cholesterol back to the liver, play an essential role in innate immunity. Indeed, they are able to bind and neutralize lipopolysaccharide (LPS) released by Gram-negative bacteria, by transporting important molecules, such as vitamin E. HDL concentration in healthy calves is lower than in adults and decreases more sharply in calves with inflammation (Giordano et al., 2017).

Albumin is the main source of amino acids and is considered as a marker of protein reserve (Ignacio de Ulibarri et al., 2005; Marcato et al., 2018). This parameter increases in dehydrated calves and decreases in cows suffering from severe infection or undernutrition (Marcato et al., 2018). There are few studies on the kinetics of albumin in calves and its use as a prognostic factor (Pardon et al., 2015; Trefz et al., 2023). In children, albumin can be used as a nutritional marker in cancer patients. In the same study, although the difference is not significant, children with cancer who developed complications had lower levels of albumin than those who did not (Milaniuk et al., 2024).

In human studies, and also in adult cattle, it has been clearly demonstrated that nutritional status influences morbidity and outcome, with adequate nutritional status leading to better patient recovery or health (Butler, 2000; Grummer, 2008; Huang et al., 2024; Ignacio de Ulibarri et al., 2005; Sordillo, 2016; Xu et al., 2024). In a context of metabolic adaptation following severe protein-calorie malnutrition, calves would be expected to show hypocholesterolemia, hypoalbuminemia and hyperuremia. These changes would explain the saturation of carbohydrate metabolism in favor of lipid metabolism and protein catabolism. In very terminal cases, hypo-uraemia could be added to the clinical picture. Urea, cholesterol and albumin are serum parameters commonly tested in routine laboratories in bovine veterinary medicine.

Belgian Blue calves were selected due to their high metabolic requirement linked to the double muscling genetic trait, making them a relevant population for assessing nutritional prognostic markers. This study compares serum albumin, cholesterol and urea levels of Belgian Blue calves on admission to hospital. The aim of studying these parameters is to detect whether differences are observable between surviving and non-surviving calves, and therefore whether the calf's nutritional status influences its outcome.

2. Material and methods

This study was carried out on calves referred to the University Veterinary Clinic for Ruminants of the Faculty of Veterinary Medicine of Liège. It was considered as a non-experimental protocol because all samples involved in this study were collected as part of the diagnosis procedure. This study was approved by the Ethics Committee of the University of Liège (Approval No: 25–2787). Informed consent was obtained from all calf owners.

Calves enrolled in this study were Belgian Blue breed and aged between 0 and 3 months, coming to the clinic for any disease requiring hospitalization. Calves with urinary disease were excluded to prevent confounding effects, as renal dysfunction can independently elevate urea levels, potentially skewing the Calf-CONUT ratio. Congenital joint stiffness and fractures were never hospitalized, they were discarded from this study. These cases were excluded from the study because they did not spend any time in hospital and were simply hospital consultations before returning to their farms. Calves included in the study were free of bovine viral diarrhea (BVD) and bovine rhinotracheitis (IBR).

Upon arrival at the clinic, a complete physical examination and the required further examinations to diagnose calves' disease were carried out. A blood sample (plain tube,Vacutainer® with a 22 G needle) was collected upon receipt of the calf as a standard routine procedure to assess the serum concentration of urea (immunochemistry, Alinity C, Abbott®) cholesterol (immunochemistry, Alinity C, Abbott®), albumin (immunochemistry, Alinity C, Abbott®). When it was doable and required, a second blood test to measure the same parameters are carried out just before the calf is discharged or euthanized. The calves were classified according to the purpose of their hospitalization as "survivor" (S) or "non-survivor" (NS).

During hospitalization, calves were fed with milk replacer (Celtilait Premio®, Table 1) at 10–15 % of their body weight. This amount was adapted according to the appetite of each calf. The concentration used was 150 g of milk powder/liter.

In addition to single values of the blood parameters, urea/albumin ratio was calculated as the "Calf-CONUT ratio" allowing as to set a prognosis threshold value.

R software (4.3.3) was used to carry out the statistical analysis of the data. A sample size calculation was performed using a power of 80 %, an expected mortality rate of 50 %, and a confidence level of 95 %, yielding a minimum required sample of 62 calves (31 each group). A Shapiro-Wilk test indicated that urea, cholesterol and albumin values were not normally distributed ($p < 0.001$). The mean and median of these same sets were also observed to validate the Shapiro-Wilk test. As a result, a non-parametric Wilcoxon rank-sum test was used instead of a paired *t*-test for the blood parameters between entry and discharge. A Levene's test confirmed unequal variances of urea ($p = 0.02$), but not for cholesterol and albumin; therefore, Welch's *t*-test was used for urea instead of Student's *t*-test to compare the result of blood parameters. Statistical tests were interpreted as significant if the p-value < 0.05. In order to determine a threshold value for the different parameters observed, a ROC curve was carried out. The ROC curve was drawn by calculating the sensitivity and specificity values. Using these cumulative parameters, the area under the curve (AUC) was also calculated to determine the predictive value of the test (cut-off value) by maximizing the Youden's index. The 5-step scale presented by Nahm (2022) was used to interpret it. The ROC curves were also used to derive sensitivities and specificities for these threshold values. The relative risk (RR) and the OR were then calculated for the cut-off values obtained. Finally, a multivariate logistic regression to adjust odds ratios (ORs) according to several potentially confounding variables was performed, taking into

Table 1

Composition and general analytical components of milk replacer (Celtilait Premio ®).

Composition	Skimmed milk, whey, palm oil, buttermilk, coconut oil, wheat protein, wheat flour, sodium chloride, rapeseed oil, wheat starch, magnesium sulphate, magnesium hydroxide, calcium carbonate
Crude protein	22 %
Crude fat	18.5 %
Crude fiber	0.1 %
Crude ashes	7 %
Calcium	0.7 %
Phosphorus	0.7 %
Sodium	0.6 %

account the parameters Calf-CONUT ratio, outcome, sex, age, weight and reason for hospitalization.

3. Results

3.1. Population

The study enrolled 82 Belgian Blue calves (46 males and 36 females) hospitalized for the following conditions: neonatal enteritis (category "digestive medicine"; 30/82); arthritis (locomotor; 18/82); digestive obstruction requiring surgery (digestive surgery; 10/82); omphalitis (other; 4/82); bronchopneumonia (respiratory; 7/82); periarthritis (locomotor; 3/82); laryngitis (respiratory; 2/82); congenital acute distress respiratory syndrome (respiratory; 2/82); abomasum ulcer (digestive medicine; 2/82), macroglossia (digestive medicine; 1/82), peritonitis (other; 1/82); vertebral abscess (locomotor; 1/82); scabies (other; 1/82). Their average age of calves is 33 ± 27 days (min. 2 – max. 90 days) and their average weight is 58 ± 19 kg (min. 20 – max. 121 kg)

Among the cohort, 47 calves were discharged alive (S), 21 females and 26 males. Thirty-five calves were euthanized during hospitalization (NS), 20 males and 15 females. Mean age was statistically different between S and NS, mean age of group S was lower than that of NS group (S= 28.19 days; NS= 40.63 days; p value=0.04). Correspondingly, the average weight was lower in group S, but difference was not statistically significant (S= 56.66 kg; NS=60.69 kg; p value>0.1).

3.2. Blood parameters

The average level and standard deviations of blood parameters for the calves involved in this study at admission and discharge are displayed in Table 2.

Table 2
Blood parameters (means ± standard deviation [median; CI 95 %]) at entry and discharge for all calves, survivor calves and non-survivor calves.

	Calves (n = 82)	Survivor calves (group S) n = 47/82	Non-survivor calves (group NS) n = 35/82
ENTRY samples (82 calves)			
Urea mg/dL	50.90 ± 36.77	43.36 ± 29.35^{a}	61.03 ± 43.27^{a}
mmol/L	18.18 ± 6.97 [15.17; CI 95 % 12.5 – 18.74]	15.48 ± 10.48^{a} [13.57; CI 95 % 11.07–17.14]	21.79 ± 15.45^{a} [18.21; CI 95 % 11.07–24.99]
Cholesterol	63.80 ± 37.30	67.30 ± 38.41	59.11 ± 35.77
mg/dL	1.65 ± 0.96	1.74 ± 0.99	1.53 ± 0.92
mmol/L	[1.53; CI 95 % 1.1–1.87]	[1.45; CI 95 % 0.91–1.63]	[1.73; CI 95 % 1.06–2.07]
Albumin (g/L)	25.57 ± 4.38 [26; CI 95 % 25–27]	26.49 ± 4.19^{b} [26; CI 95 % 26–27]	24.34 ± 4.39^{b} [25; CI 95 % 23–27]
Urea (mg/dL) / albumin (g/L)	1.96 ± 1.30	1.63 ± 0.99^{c}	2.41 ± 1.53^{c}
DISCHARGE/dead/euthanized samples (23 calves)			
	All calves n = 23/82	Survivor calves (group S) n = 15/82	Non-survivor calves (group NS) n = 8/82
Urea	26.78 ± 37.25	15.27 ± 8.59^{d}	48.38 ± 58.28
mg/dL	9.56 ± 13.30	5.45 ± 3.06^{d}	17.28 ± 20.81
mmol/L	[5.71; CI 95 % 4.28 – 8.92]	[4.28; CI 95 % 2.86–6.78]	[12.67; CI 95 % 5.18–16.42]
Cholesterol	77.96 ± 26.12	84.53 ± 21.43^{d}	65.63 ± 36.06
mg/dL	2.02 ± 0.73	2.19 ± 0.55^{d}	1.70 ± 0.93
mmol/L	[2.09; CI 95 % 1.94–2.30]	[2.25; CI 95 % 1.94–2.51]	[2.03; CI 95 % 0.75 – 2.09]
Albumin (g/L)	23.78 ± 2.59 [24; CI 95 % 22–25]	24.27 ± 2.76^{d} [25; CI 95 % 23–26]	22.88 ± 2.10 [22.5; CI 95 % 21–24]
Urea (mg/dL) /albumin (g/L)	1.14 ± 1.56	0.63 ± 0.36^{d}	2.09 ± 2.41

Serum urea and albumin levels at admission and discharge. Survivors exhibited lower urea and higher albumin at admission, suggesting better nutritional status upon hospitalization. n = number of calves; ^{a},^{b},^{c} significant difference (p value<0.05); ^{d} significant difference at paired *t*-test between entry and discharge values (p value<0.05).

Of the 82 calves in the cohort, only 23 calves were sampled at the day of entrance and before discharge/euthanasia/death; 15/23 of these calves had recovered and returned to the farm, while 8/23 were euthanized or died during hospitalization.

Urea (adult cow normal range: 3.5–7.1 mmol/L) (Divers, 2018) and albumin (S: 26.49 ± 4.19 g/L; NS: 24.34 ± 4.39 g/L; reference range: 31.7 ± 4.6 g/L) (Guyot et al., 2024) levels at entry are above normal values in both group S and NS (Divers, 2018). Cholesterol levels at admission were below the normal range for pre-calving cows in both groups (S: 1.74 ± 0.99 mmol/L; NS: 1.53 ± 0.92 mmol/L; reference range for pre-calving cows: 2.21 ± 0.08 mmol/L) (Gueorguieva and Gueorguiev, 1997).

At the day of admission, although the S group had higher cholesterol concentrations, no significant difference was noticed in cholesterol concentrations (Student *t*-test p value >0.1) between S and NS groups. Albumin concentration is significantly higher in group S than in group NS (Student *t*-test p value= 0.02). In contrast, the urea level was significantly higher in group NS than group S (Wech's *t*-test p value = 0.04).

The comparison of parameters' values at entry and discharge showed that the group S has a significant increase in cholesterol (p < 0.05) and a significant decrease in urea (p < 0.01) and albumin (p < 0.05).

Wilcoxon rank sum test was used to compare the values of calves with blood samples taken at entry and discharge, the results show that serum urea (p value=0.0007) and albumin (p value=0.007) are significantly higher for group S at the entry (Table 2). Cholesterol levels were significantly lower (p value=0.003) at entry than at discharge for group S. In Group NS, albumin was significantly lower (p value=0.02) at entry.

The predictive value of the serum albumin result at entry was evaluated. Fig. 1 shows a ROC curve for calf albumin at entry. The ROC curve does not show a clear cut-off value and the calculated area under the curve (AUC) was 0.398 (95 % CI 0.28–0.52). The extracted threshold is 29 g/L but cannot be considered a threshold value because the AUC is too low and the test is considered non-predictive.

3.3. Calf-CONUT ratio

The urea/albumin ratio at entry was significantly higher in group NS than in group S (p value = 0.01; Table 2). Fig. 2 shows the ROC curve for the albumin/urea ratio. The AUC was 0.64 (95 % CI: 0.52–0.77). The cutoff value of 2.64 was chosen based on Youden's index, maximizing the sum of sensitivity (46 %) and specificity (87 %). However, alternate cutoffs of 2.5 and 2.7 were also tested, showing minor differences in predictive accuracy (Fig. 2). Above the threshold of 2.64, the OR to die is 5.75 (95 % CI: 1.93–17.92). The RR of non-survival is 2.29 (95 % CI: 1.46–3.60).

A multivariate logistic regression model adjusting for age, weight, sex and reason of hospitalization (digestive medical, digestive surgery, locomotor, respiratory, others) showed that the Calf-CONUT ratio remained a significant predictor of mortality (OR = 0.316, p = 0.000537), suggesting that malnutrition independently contributes to prognosis. Age, weight, sex and reason for hospitalization did not influence animal outcome (p > 0.1).

3.4. Calf-CONUT ratio in neonatal enteritis

In the group of calves with enteritis (n = 30), there were 24 surviving calves and 6 non-surviving calves. A ROC curve analysis showed an area under the curve (AUC) of 0.785 (95 % CI: 0.55–1). The cutoff value of 2.85 was chosen based on Youden's index, maximizing the sum of sensitivity (83 %) and specificity (78 %). However, alternate cutoffs

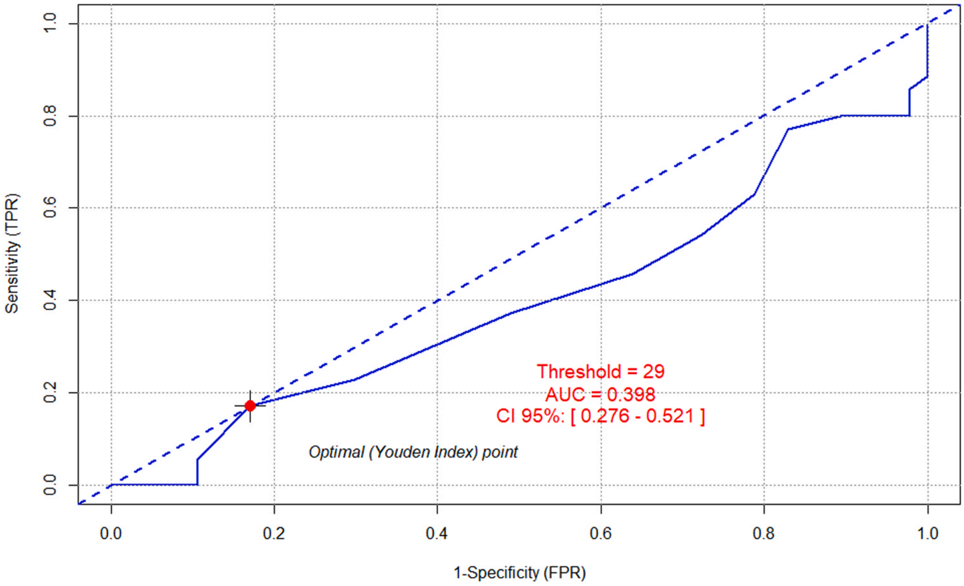

Fig. 1. ROC curve of the serum concentration of albumin of all calves (n = 82) at entry. No cutoff value could be determined and the AUC of 0.398 (95 % CI 0.28–0.52) demonstrates no relationship.

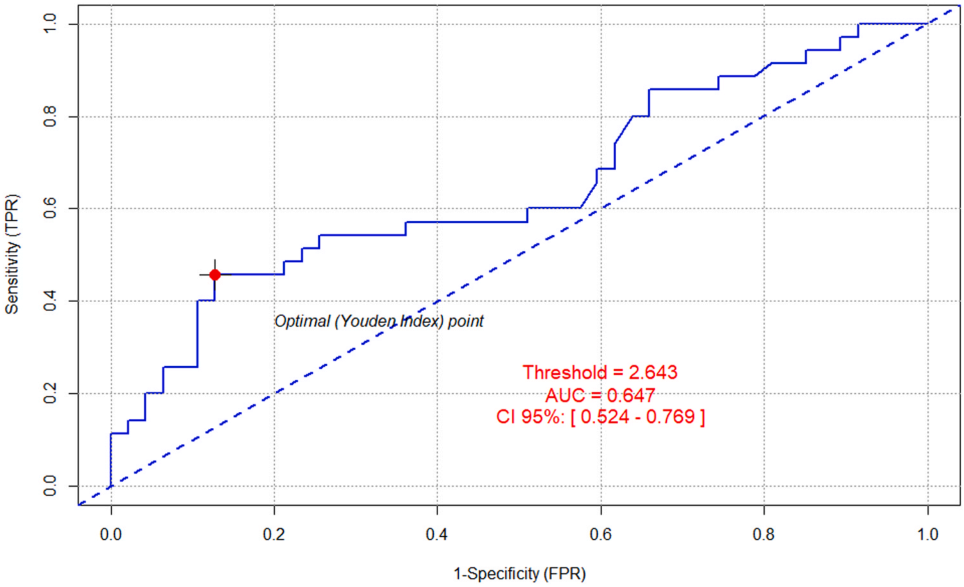

Fig. 2. ROC curve of the ratio urea/albumin of all calves (n = 82) at entry. The red point represents the best predictive value (cutoff) on the curve. This curve presents an area under the curve (AUC) of 0.647 (95 % CI: 0.52–0.77).

of 2.7 and 2.9 were also tested, showing minor differences in predictive accuracy (Fig. 3). The threshold value of the ROC curve is set at 2.85. Calves suffering from enteritis and presenting a Calf-CONUT ratio greater than 2.85 had a non-survival RR of 10 (95 % CI: 1.34–74.51) and an OR of 19 (95 % CI: 1.85–470.91).

4. Discussion

In rural veterinary medicine, where economic considerations are of significant importance, it is crucial to provide a reliable prognosis. Indeed, measuring blood urea and albumin levels at the time of its initial examination will allow to predict the animal's outcome. The Calf-CONUT ratio could also serve as a preventive tool for assessing the nutritional status of calves on a farm. It could be integrated into routine bloodwork for hospitalized calves, enabling veterinarians to identify at-risk animals early and adjust nutritional support strategies accordingly. A calf with a urea-to-albumin ratio greater than 2.64 is two times more likely to die (RR = 2.29, 95 % CI: 1.46–3.60; OR = 5.75, 95 % CI: 1.93–17.92), regardless of the disease. However, the ROC curve analysis yielded an AUC of 0.64 (95 % CI: 0.52–0.77), indicating poor-to-fair predictive ability. Given the low sensitivity (46 %), the Calf-CONUT ratio should be used in combination with other clinical indicators. In fact, for a model to be a predictive model, the condition is that the AUC must be greater than 0.7 (Nahm, 2022). The loss of sensitivity could be explained by the small number of animals involved and the variety of diseases endured by the calves.

Urea levels are above normal values in both group S and NS (S: 15.48 ± 10.48 mmol/L; NS: 21.79 ± 15.45 mmol/L; adult cow normal range: 3.5–7.1 mmol/L) (Knowles et al., 2000; Divers, 2018), with group S showing significantly lower concentrations than group NS. In addition,

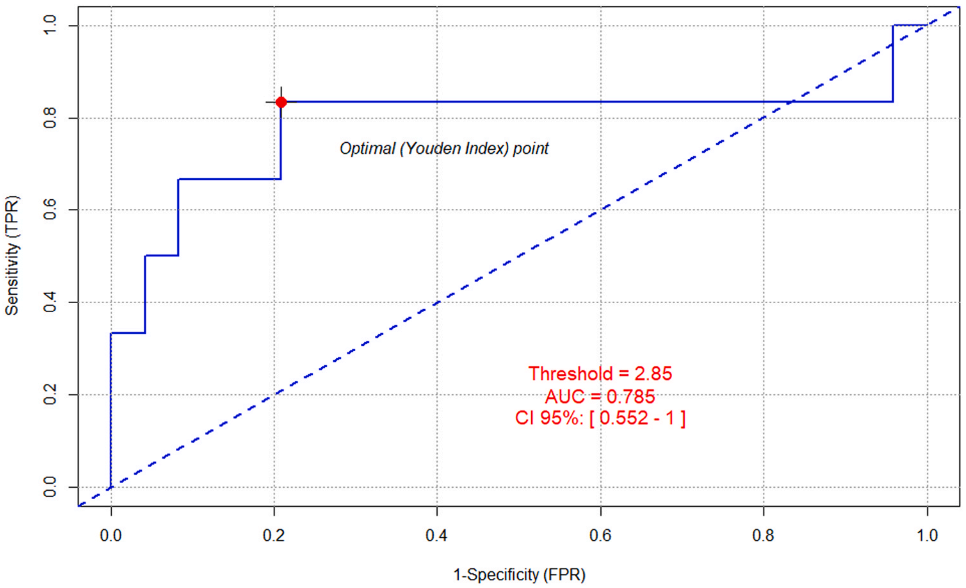

Fig. 3. ROC curve of the ratio urea/albumin of calves with enteritis (n = 30) at entry. The point represents the best predictive value (cutoff) is in red on the curve. This curve presents an area under the curve (AUC) of 0.785 (95 % CI: 0.55–1).

urea levels in calves are lower than in adults up to 83 days of age (Knowles et al., 2000), making this increase even more significant for calves. In calves with neonatal diarrhea, urea has previously been used as a renal parameter to compare survivors with non-survivors (Yanar et al., 2023). Both groups exhibited elevated urea levels, but non-survivors had statistically higher uremia than survivors. This suggests that renal function alone may not account for the increased uremia observed in these calves. In fact, during starvation, glycogen reserves are depleted rapidly (within a few hours), and uremia becomes apparent within 2–5 days. This urea is derived from the degradation of L-alanine in the liver to synthesize pyruvate, with urea serving as an intermediate product of this process (Palmer and Clegg, 2021). High urea levels would, therefore, indicate a recent negative energy balance

In calves, albumin concentration is correlated with diet (Boorboor et al., 2020). For many years, albumin has been used in human medicine as the main marker of patient nutrition. However, albumin (and pre-albumin) is also a marker of inflammation, and is reported to correlate negatively with the severity of inflammation (Evans et al., 2021). The return to physiological values could be attributed to the resolution of inflammation, a reduction in metabolic energy and protein requirements, a transition to anabolism or a reduction in nutritional risk (Evans et al., 2021). A recent study compared the biochemical parameters of two breeds, the Belgian Blue (BB) and the Holstein Friesian (HF), and found that serum albumin concentration was lower in BB cows (BB: 31.7 ± 4.6 g/L; HF: 38.5 ± 2.8 g/L) (Guyot et al., 2024). This study was limited to Belgian Blue calves, and caution is advised when applying these findings to other breeds with different metabolic characteristics. In our study, the average albumin concentrations for all calves at entry were below the range described by Guyot and colleagues for Belgian blue calves (S: 26.49 ± 4.19 g/L; NS: 24.34 ± 4.39 g/L; reference range: 31.7 ± 4.6 g/L), with group NS showing significantly lower levels than group S (p-value = 0.02).

The presence of high uremia and low albumin in the animals upon arrival indicates that they were already in an advanced stage of starvation (lasting several days) at the time of hospital admission. This is not surprising, as the Ruminant Clinic at the University of Liège typically handles second-line cases, often referred after the failure of first line treatment.

The urea/albumin ratio was calculated on the basis of urea values in mg/dL instead mmol/L, since this is the unit most widely used by Belgian reference laboratories, to enable the practitioner to easily implement this score in practice. In human medicine, the CONUT score is widely used to predict the short- and long-term outcome of many diseases, (Di Vincenzo et al., 2023; Liu et al., 2023; Xu et al., 2024). Regardless of the primary disease, this score is systematically associated with treatment outcome. However, it is possible to implement the score value for specific calf diseases as well. For this reason, the ROC curve was also drawn for neonatal enteritis (Fig. 3), as this condition concerned a third of the population studied. The latter was much more representative, with a clear cutoff of 2.85 and an AUC of 0.785 (95 % CI: 0.55–1). In this case, the model is considered to be a fair predictive model (AUC between 0.7 and 0.8) (Nahm, 2022). This model express a sensitivity of 83 % and a specificity of 78 %. Enteritis calves with a Calf-CONUT ratio greater than 2.85 had an RR of 10 (95 % CI: 1.34–74.51) and an OR of 19 (95 % CI: 1.85–470.91), but with very wide confidence intervals, so these values must be interpreted with caution. It is reasonable to suspect that, as with the Calf-CONUT calculated on the whole calf population, the RR and the OR are greater than 1, and that the very high values obtained are certainly linked to the very small population studied (n = 30). Nonetheless, by adapting the threshold values for enteritis, it is possible to improve the specificity and sensitivity of the test. It's a safe bet that if a larger population affected by the same disease was studied, it would be possible to establish more appropriate Calf-CONUT threshold values with good sensitivity and specificity.

The calf groups are statistically comparable in terms of male-to-female ratio and weight. However, Group S consists of significantly younger calves compared to Group NS (S = 28.19 days; NS = 40.63 days; p-value = 0.04). The fact that this difference is based on age rather than weight suggests that the calves in Group NS may have experienced stunted growth. Additionally, the older age of Group NS calves could indicate a higher prevalence of chronic diseases, which directly contribute to malnutrition.

Another important aspect to consider in this study is how the calves were fed prior to hospitalization. The composition of the milk replacer, particularly its fatty acid profile, can influence cholesterol levels. For instance, a milk replacer rich in polyunsaturated fatty acids (such as soybean oil or coconut oil) can lead to hypercholesterolemia and fatty liver in preruminant calves (Hocquette and Bauchart, 1999). Additionally, the composition of the milk replacer used in the clinic (primarily skimmed milk and whey, but also containing palm oil and coconut oil) may have influenced the calves' cholesterol levels at discharge, as cholesterol was significantly higher at discharge than at admission (Hocquette and Bauchart, 1999).

There is also evidence that certain diseases, such as pneumonia caused by *Mannheimia haemolytica*, can alter the function of the enzyme lecithin cholesterol acyltransferase (LCAT), leading to a decrease in serum cholesterol during such infections. LCAT activity is known to be influenced by various factors: it decreases in dairy cows with a negative energy balance, is inhibited by bacterial lipopolysaccharides, and increases with the administration of anti-inflammatory glucocorticoids. As a result, interpreting cholesterol levels is complex and must be done on a case-by-case basis or within groups of highly homogeneous cases to draw meaningful conclusions (Nakagawa and Katoh, 2001, 1999).

In our study, cholesterol levels at admission were below the normal range for pre-calving cows in both groups (S: 1.74 ± 0.99 mmol/L; NS: 1.53 ± 0.92 mmol/L; reference range for pre-calving cows: 2.21 ± 0.08 mmol/L)(Gueorguieva and Gueorguiev, 1997). No significant difference was observed between the two groups. Given the various illnesses for which the calves were admitted, it is challenging to determine whether the drop in cholesterol is attributable to infection, malnutrition, or a combination of both (Hocquette and Bauchart, 1999; Nakagawa and Katoh, 1999, 2001).

A strength of this study is the inclusion of a sufficient number of calves in both groups S and NS, as well as the ability to homogenize the groups to include a variety of diseases in each. Given the specificities of the energy metabolism of pre-ruminants (Hocquette and Bauchart, 1999), it was also crucial to limit the study to unweaned calves.

Additionally, blood sampling at discharge or prior to the calf's death proved valuable. It allowed us to observe an improvement in the nutritional status of surviving calves, particularly regarding urea and cholesterol levels (Table 2). However, albumin levels decreased during hospitalization, which was expected given its slower kinetics—it takes several weeks for albumin levels to change (Musimwa et al., 2015; Whicher and Spence, 1987). Furthermore, studies in humans have shown that an increase in albumin levels within seven days of nutritional support cannot be attributed to improved nutritional status but rather to the resolution of underlying inflammation (Boesiger et al., 2023). Although the total sample size was 82, only 23 calves had complete admission and discharge data, reducing statistical power for within-calf analysis.

This phenomenon is also observed in group NS, where urea and cholesterol remain elevated prior to death, while albumin decreases by approximately 2 g/L. This highlights that albumin alone cannot be used as a prognostic factor in calves (specificity: 43 %; sensitivity: 36 %) and should be combined with urea for better reliability.

A limitation of this study is the lack of detailed information about the calves' history, particularly whether they experienced multiple illnesses prior to hospitalization. Another limitation of this study evaluates in-hospital mortality but does not account for long-term calf health post-discharge. Nonetheless, the calves were discharged only after complete resolution of their symptoms and any complications that arose during hospitalization. Having a test that assists owners in making short-term decisions about whether it is worthwhile to invest in treating their calves is, however, an important first step. Future research should assess survival beyond hospitalization.

This study paves the way for future research on the use of biochemical parameters in calf disease prevention. For instance, calves of the same breed, raised on the same farm under identical conditions, could be monitored from birth to examine the relationship between these biochemical parameters and disease risk. Variations in these parameters could be linked to specific events experienced by the calf, such as stress or dietary changes. Additionally, this ratio could be further explored by studying a larger number of calves from homogeneous breeds affected by the same type of disease (e.g., enteritis, pneumonia). Long-term calf survival could also be evaluated. Finally, nutritional assessments could be conducted by comparing the Calf-CONUT ratio in calves fed either milk replacer or whole milk to determine whether their nutritional status differs under equivalent feeding conditions.

5. Conclusion

In conclusion, significant differences in blood concentrations of urea, cholesterol, and albumin are evident in calves either at admission or at the end of hospitalization, and these differences are associated with the calves' prognosis. Similar to the CONUT approach used in human medicine, the nutritional status of calves can be evaluated using the urea/albumin ratio (Calf-CONUT ratio). This method demonstrates a RR of 2.29 (95 % CI: 1.46–3.60) for mortality during hospitalization, all diseases combined (OR=5.75, 95 % CI: 1.93–17.92), if the ratio is greater than 2.64. While this ratio demonstrated high specificity (87 %), its low sensitivity (46 %) limits its standalone use. Nevertheless, it provides an objective measure of the calves' nutritional status upon arrival and aids in refining their prognosis. Early identification of at-risk calves using the Calf-CONUT ratio could facilitate targeted nutritional interventions, reducing disease severity and improving survival outcomes. However, further studies focusing on specific diseases are needed to enhance the sensitivity and specificity of this test and additional markers should be explored to enhance predictive accuracy.

CRediT authorship contribution statement

Théron Léonard: Writing – review & editing, Data curation, Conceptualization. **Rao Anne-Sophie:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Djebala Salem:** Writing – review & editing, Formal analysis, Data curation. **Bayrou Calixte:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization. **Casalta Hélène:** Writing – review & editing, Formal analysis, Data curation. **Borelli Elena:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Van Leeuw Corine:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Eppe Justine:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

the authors would like to thank all those who made this study possible.

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