2015 IEEE Symposium Series on Computational Intelligence

Fuzzy Set-Based Detection of Hypotension Episodes for Predicting Leaks in Sleeve Gastrectomy

J. B. R. Visser*, A. M. Wilbik†, U. Kaymak†
Information Systems, School of Industrial Engineering
Eindhoven University of Technology, Eindhoven, The Netherlands
Email: *j.b.r.visser@student.tue.nl, †{a.m.wilbik, u.kaymak}@tue.nl

S. W. Nienhuijs
Department of Surgery,
Catharina Hospital, Eindhoven, The Netherlands
Email: simon.nienhuijs@catharinaziekenhuis.nl

***Abstract*—This paper utilizes a fuzzy sets approach for the analysis of arterial blood pressure and detection of hypotension episodes during sleeve gastrectomy surgery. Membership of systolic blood pressure measurements to the set of "low systolic blood pressure" is used for feature construction of predictive variables in predicting leakage after a sleeve gastrectomy procedure. The prediction task is posed as a classification problem. Logistic regression and Takagi–Sugeno fuzzy inference systems are used as the classification tools. Results indicate an increase in predictive performance compared to previous studies using the same data set.**

I. Introduction

Nowadays hospitals are dealing with an increasing amount of patients demanding more complex surgical procedures than ever before. A particularly important branch of procedures is bariatric surgery since obesity is a growing global health problem. Sedentary lifestyles and a fast food culture have worsened this problem year after year. Besides the obvious aesthetic problems, obesity can lead to physical and psychological problems like depression, heart disease, diabetes, cancer and osteoarthritis [1].

One of the most common procedures within bariatric surgery is the laparoscopic sleeve gastrectomy. In this procedure, the stomach is reduced to 75-85% of its original size and made into the shape of a tube or sleeve. Sleeve gastrectomy (SG) has recently been recognized as a safe and effective stand-alone bariatric procedure, achieving a significant reduction in weight and comorbidities [2], [3]. The overall complication rate of SGs is lower than 15% [4].

The most common complications after the procedure are abscesses and leakages along the stapler lines. The leakage rate after laparoscopic sleeve gastrectomy is around 2.2% [5]. The management of early leakage should not be delayed and is most effectively treated by operative or percuraneous drainage and endoscopic stenting [6].

There are some studies trying to predict leakage after colorectal cancer surgery by finding the risk factors such as intraoperative blood pressure [7]. Nevertheless, these kinds of studies do not focus on measuring the performance of possible predictive models. More importantly, they do not study leaks after bariatric surgery, specifically. In this paper, we are focusing on leaks after bariatric surgery, based on the previous works of [8], [9].

Our focus is on investigating the influence of occurrence of hypotension episodes during the procedures on the leakage. Hypotension episode occurs when the arterial blood pressure is below a certain threshold for a predefined period of time. The threshold values used in the definition of the hypotension episode were investigated in [10]. In previous work [8], [11], it was stated that presence of a hypotension episode is a good predictor variable for leakage prediction. In these studies, a hypotension episode is defined in a crisp way, as a period of time where the blood pressure falls below a chosen threshold for longer than a given time period. However, such a crisp definition is not necessarily relevant from a clinical perspective, since the transition into a low blood pressure episode is typically gradual. Therefore, we propose to use a fuzzy set-based representation of low blood pressure episodes.

In this paper we investigate whether a fuzzy set-based detection of low blood pressure episodes by using additional features describing length and severeness of this episode have predictive value. We tested our method on data from patients who have had laparoscopic sleeve gastrectomy between 2006 and 2012 at the Catharina Hospital in Eindhoven, the Netherlands. The data contain pre-operative information about patients as well as intra-operative blood pressure measurements.

The outline of the paper is as follows. In Section II, we give the background information regarding the problem, as well as report previous results. We present our method for fuzzy description of the hypotension episodes in Section III. In Section IV, we discuss the experimental setup and the results we obtained. The paper ends with conclusions in Section V.

II. Background

The problem of anastomotic failure after Laparoscopic Sleeve Gastrectomy has been investigated in [11], [8], [9]. In [11], the authors investigated the influence of the occurrence of hypotension episodes for the leakage prediction. The conclusion of this work was that episodes of systolic blood pressure below 100 mmHg for 15 or 20 minutes are related to the leakage. The authors also discovered that mean blood pressure below 70 mmHg lasting for 20 minutes can be also a good predictor of leaks. Similar episodes of 15 minutes had less predictive value.

978-1-4799-7560-0/15 $31.00 © 2015 IEEE
DOI 10.1109/SSCI.2015.192

TABLE I
SIGNIFICANT VARIABLES FOR LEAK PREDICTION.

Variable	Description
Smoking	**Categorical** – shows if a patient is a regular smoker or not. Patients with failure smoke more often.
Puffs	**Categorical** – shows if the patient uses puffs for lung problems or not. Patients with failure use puffs more often.
Antacids	**Categorical** – shows if the patient uses antacids for stomach problems or not. Patients with failure use antacids more often.
Track type	**Categorical** – shows if a patient had the fast-track or normal-track approach for the procedure. Fast-track is used since January 2011 instead of the normal-track. Failure occurs less with the fast-track procedure.
Approach type	**Categorical** – either *Laparoscopic* or *Conversion* or *Open* approach. Laparoscopic approach means that the procedure is done with small incisions. Failure occurs less with this approach. Conversion approach shows if patients had a second procedure or revision. Open approach means that a large surgical cut is used for the procedure. Failure occurs more often with the two later approaches.
Stapler type	**Categorical** – Endo GAITM stapler was used before December 2009. Failure occurs more often with this staple technique. TRI-stapleTM stapler is used since May 2010. Failure occurs less often with this staple technique.
Duration	**Continuous** – the length of the procedure in minutes

In [8], the significant variables regarding patients' and procedure's characteristics were investigated for predicting the occurrence of leaks. The variables identified as relevant in this study are shown in Table I. In [9], the author focused on better detection of hypotension episodes and finding the optimal thresholds for defining the hypotension episode for leakage prediction. Since the blood pressure measurements are not continuous, and measured usually every 2 to 5 minutes during the operation, the exact start and end of a low blood pressure episode are unknown. Consequently, finding the exact duration of the hypotension episodes is not possible. In [9] different methods for estimating the duration of episode were tested, and it was found that linear interpolation in between the measurements has predictive value. Additionally, different threshold values for blood pressure and duration were investigated in order to include binary information regarding the presence of a hypotension episode.

Afterwards, a logistic regression model was used to predict leakage. The best results were obtained for a systolic pressure threshold of 100 mmHg for a duration of at least 10 or 15 minutes. However, a threshold of 90 mmHg did not perform much worse. The accuracy was around 78%, with precision and recall equal to 67% and 39%, respectively. Cohen's kappa was 39% and AUC (area under the ROC) was 80%.

III. METHOD

The work in [9] assumed that a hypotension episode occurs when the arterial blood pressure is below a certain threshold for a predefined period of time. However, the low blood pressure episode is gradual and it is not possible to determine an optimal threshold for defining the threshold. Therefore, we

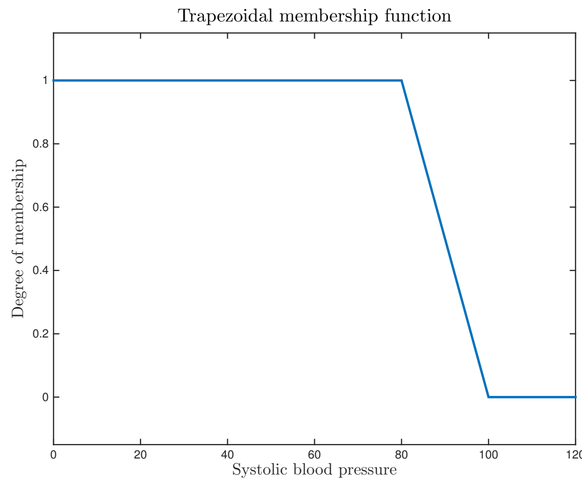

Fig. 1. Membership function for low systolic blood pressure.

propose to use a fuzzy set-based definition of the episodes by using new features that capture the length and severeness of the hypotension episode in order to account for the gradual character of the episodes.

Previous work [9] showed that the threshold for the systolic blood pressure for the hypotension episode should be between 90 and 100 mmHg, *i.e.* such episodes have biggest predictive capabilities. Based on this information and after some experimentation, we decided to define *low* blood pressure as a fuzzy set over the domain of systolic blood pressure. The membership function is a left-shouldered trapezoidal function (Z-function) where the membership decreases linearly from 1 to 0 in the rage 80 to 100 mmHg. Fig.1 shows the membership function for *low* blood pressure.

By using the membership function in Fig.1, we are able to determine to which degree each blood pressure measurement belongs to the set of low blood pressures. In other words, let us assume that s_t, $t = 1, 2, \ldots \ldots$ represents the time series of the systolic blood pressure. The result of this transformation is the time series p_t^{low}, $t = 1, 2, \ldots \ldots$, such that

$$p_t^{low} = \mu_{low}(s_t). \tag{1}$$

Given the time series p_t^{low}, the length of an interval during which the blood pressure is *low* can be computed as the time integral of $\mu_{low}(s_t)$. Ideally, this integral would be calculated analytically. However, the time series does not follow an analytical expression, in general. Since we have the pressure values available for a (finite) number of measurements at discrete time steps, we use the numerical integration method with the trapezoidal rule to approximate the integral. We assume that the time series that we are interpolating consists of (piecewise linear) line segments passing through the points p_t^{low}, p_{t+1}^{low}.

It is worth noting that one patient may have encountered more than one low blood pressure episode, and we capture

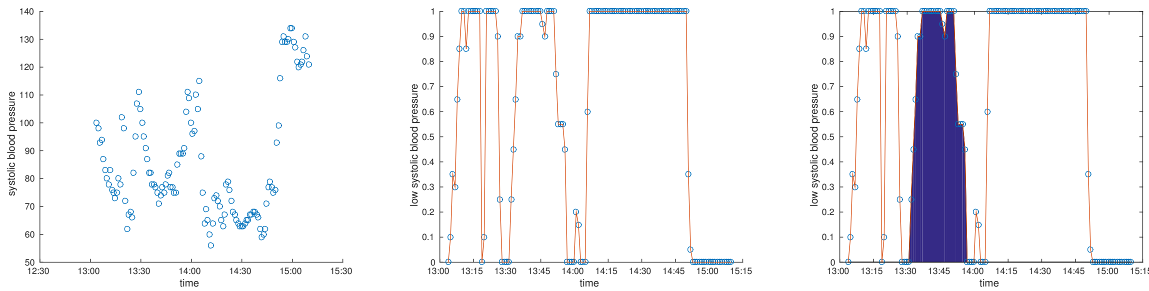

Fig. 2. Example of detecting low blood pressure episodes.

the duration of all the episodes separately. The duration d of an episode is calculated as

$$\begin{aligned} d &= \int_{t_1}^{t_2} p_t^{low} dt = \\ &= \sum_{i=t_1}^{t_2-1} (t_{i+1} - t_i) \frac{p_{i+1}^{low} + p_i^{low}}{2}, \end{aligned} \tag{2}$$

where t_1 and t_2 are beginning and end of a hypotension episode, $p_{t_1}^{low} = p_{t_2}^{low} = 0$ and $p_t^{low} > 0$ for $t \in (t_1, t_2)$.

Because a patient may experience multiple hypotension episodes during surgery, we derive the following features to be used as inputs to the prediction models:

- number of "episodes",
- maximal "duration" of the episodes,
- minimal "duration" of the episodes,
- median "duration" of the episodes,
- average "duration" of the episodes.

Figure 2 illustrates our method for determining the duration of the episodes. On the leftmost plot we can see the original systolic blood pressure measurements for a patient. The middle plot depicts the degree to which the pressure values belong to the set of *low* blood pressure, given the definition in Fig.1. Note that there are five low blood pressure episodes in Fig.2. In the right plot, the area shaded for the third episode is interpreted as the duration of the episode.

IV. Results

We tested our method on data collected from Catharina Hospital in Eindhoven, in the Netherlands. The data were collected for 1286 procedures performed from 2006 to 2012 and included 38 procedures that resulted in leakage. The data set contained all variables named in Table I as well as the additional features related to hypotension episodes discussed in Section III.

Firstly we created the validation set that contained 10% of data with the same distribution of the target class as the whole data set. The remaining data were used for the training and testing the model. In order to overcome the problem of unbalanced data, we used the synthetic minority over-sampling technique, SMOTE, introduced in [12]. Hence 300 synthetic minority class samples were generated by interpolation between existing cases. In order to better estimate the quality of the models we used commonly used 10-fold cross-validation, advocated in [13]. So 90% of the over-sampled data were used for training and 10% for testing in each fold.

We used logistic regression and Takagi–Sugeno fuzzy inference system as the classification method, for predicting whether leakage takes place or not. For both methods we used the same partition into the folds, in order to facilitate comparison. For every fold, a model was trained with the above mentioned two methods using the over-sampled data set. Afterwards, the model was evaluated with the over-sampled validation set as well as the test data set with original target class distribution.

Each model was evaluated with several performance measures: accuracy, precision, recall, AUC, Cohen's Kappa and AUK. The first three metrics can be calculated based on the confusion matrix per fold [14].

- **Accuracy** ((TP + TN) / Total): percentage of records that was classified correctly.
- **Recall** (TP / (TP+FP)): percentage of leakage detected.
- **Precision** (TP / (TP+FN)): percentage of all predicted leaks which were correct.

Herein TP stands for *true positives*, TN for *true negatives*, FP for *false positives* and FN for false negatives. Since there is a large class imbalance in the data set, Cohen's Kappa is generally thought to be a more robust measure than simple accuracy, as Kappa takes into account the agreement occurring by chance. Therefore it is considered to be more useful then accuracy for this study [15].

In addition to the above metrics that are valid at a single operating point only, the average performance of the models across different operating points is studied receiver operating characteristic (ROC) curves [16] and kappa curves [17]. The performance is quantified by using the AUC (area under ROC curve) and AUK (area under kappa curve). AUK is a metric proposed recently in order to compensate for AUC being sensitive to the class distribution [17]. Since our data set is highly imbalanced, AUK seems to be the preferred performance metric. Furthermore, kappa inherently takes into account the class skewness in the data and prefers correct classification of the minority class over the majority class.

TABLE II
RESULTS FOR OVER-SAMPLED TEST DATA SET

	Log regr. m1		Log regr. m2		FIS m1		FIS m2	
	μ	σ	μ	σ	μ	σ	μ	σ
Accuracy	0.8294	0.0238	0.8322	0.0238	0.8350	0.0224	0.8531	0.0224
Precision	0.9698	0.0120	0.9689	0.0141	0.9715	0.0218	0.9840	0.0110
Recall	0.8386	0.0165	0.8417	0.0156	0.8430	0.0179	0.8525	0.0200
AUC	0.7733	0.0478	0.7786	0.0533	0.7987	0.0460	0.8112	0.0440
Kappa	0.3567	0.1012	0.3729	0.0991	0.3795	0.1016	0.4452	0.1053
AUK	0.2042	0.0362	0.2094	0.0388	0.2228	0.0334	0.2337	0.0309

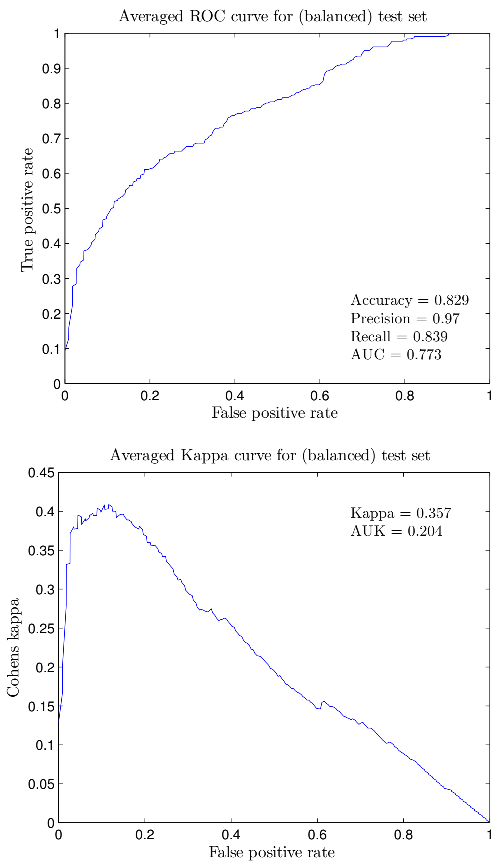

Fig. 3. Results for the logistic regression model on the over-sampled test set.

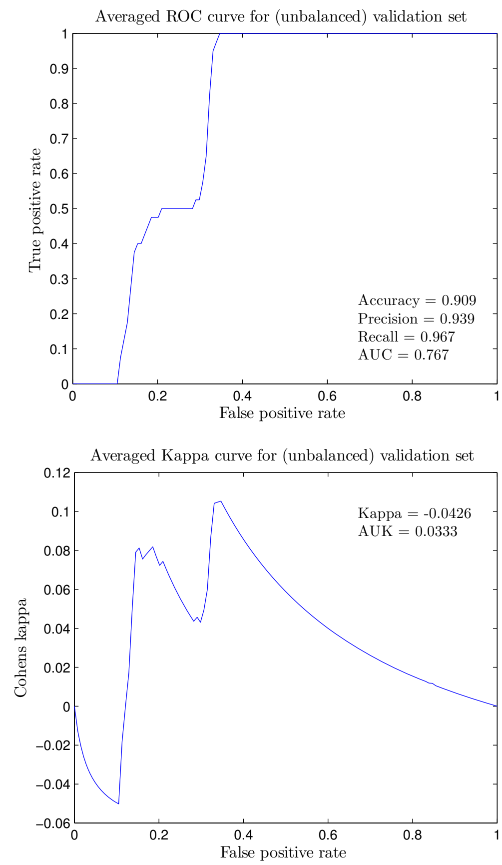

Fig. 4. Results for the logistic regression model on the unbalanced validation set.

There is a relation between ROC curves and kappa curves, which has been studied in [17]. For every fold, a model and the associated ROC and AUK curves are plotted based on the test set from over-sampled data and on the validation set from the original (imbalanced) data.

Ten-fold cross validation is used for assessing the performance of our proposed approach. Below, the presented results are the average from those 10 models. We have tested different models built using two different sets of features. The first contains only the patient and procedure characteristics smoking, puffs, antacids, track type, approach type, stapler type and duration of the surgery, *i.e.* features described in Table I. We treat this model as the benchmark model. The second feature set has all features of the first model plus the five features describing the low blood pressure episodes discussed in Section III.

Let us first discuss the results of the benchmark data set for the logistic regression model. Figure 3 shows the averaged ROC curves and kappa curves for the logistic regression model created using 10-fold cross validation on the validation (over-sampled) test set. This model performs with AUC equal to 0.77 and kappa equal to 0.35. These results are similar to the results from [9], which we use as the base case. Additional

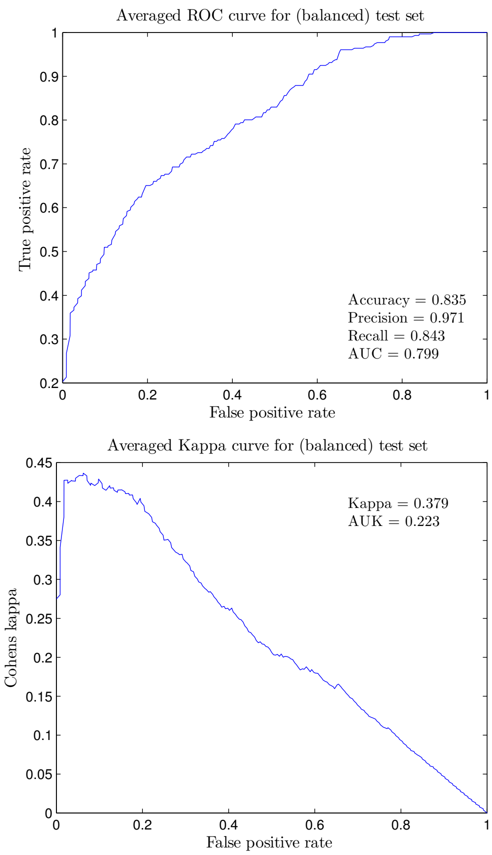

Fig. 5. Results for the FIS on the over-sampled test set.

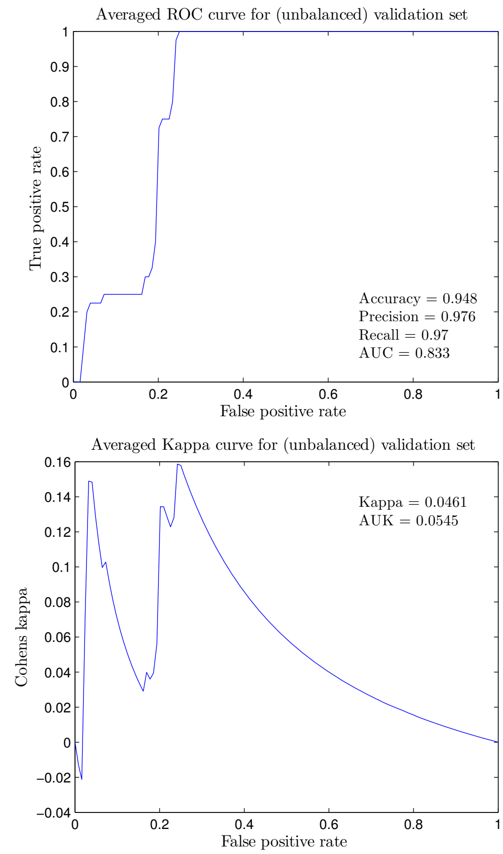

Fig. 6. Results for the FIS on the (unbalanced) validation set.

performance measures are presented in Table II for the over-sampled test set.

We assessed the performance also on the unbalanced validation set. The ROC and Kappa curves are shown in Figure 4. Note that the performance of the model on this data set is lower, which indicates that the characteristics of the validation set differ considerably from the training set. Although AUC is reasonably high, the negative value for kappa shows that the model makes significant classification errors, especially when the false positive rate is small. This is a consequence of the class imbalance in this problem. Additional performance metrics for this data set are presented in Table III.

Takagi–Sugeno (TS) models [18] have been applied successfully in various clinical problems [19], [20], [21]. They are numerically competitive models, while the fuzzy rules in the system provide an interpretable representation of the general behavior of the model, which facilitates communication with domain experts. For that reason, we looked also at a first-order Takagi–Sugeno fuzzy inference system (FIS) for this problem. To build the model, we used fuzzy c-means clustering [22] and the ANFIS (adaptive neuro-fuzzy inference system) learning method [23]. The main steps of our fuzzy modeling approach are similar to the ones described in [24]. We cluster the data in the product space of features by using fuzzy c-means. Each cluster corresponds to a rule in the FIS. We tried different different values for the number of clusters c, and came to the conlcusions that two clusters were sufficient for our data set. These clusters were used to initialize the rule base of a first-order TS model, which parameters are then optimized using ANFIS training. The FIS computes a score, which can then be used to classify the data samples into “leak” or “no leak”. Figure 5 and Fig.6 show the results for the testing and validation sets, respectively. It can be noticed that the fuzzy model has better performance than one obtained using logistic regression. The models with larger number of rules showed similar results, a bit better on the testing (over-sampled) set and a bit worse on the validation data set.

The above models are used as the benchmark with which we want to compare and measure the usefulness of the new hypotension features characterizing the low blood pressure episodes, based on detection with our fuzzy set approach. This is done in the second set of experiments.

Let us first show the results for the logistic regression models. Figure 7 and Fig.8 show the results for the testing and validation sets, respectively. We note that there are no significant improvements when we compare these results with the ones from the first set of features, since the performance measures have virtually the same values.

TABLE III
RESULTS VALIDATION DATA SET.

	Log regr. m1		Log regr. m2		FIS m1		FIS m2	
	μ	σ	μ	σ	μ	σ	μ	σ
Accuracy	0.9094	0.0055	0.9250	0.0055	0.9477	0.0053	0.9664	0.0053
Precision	0.9387	0.0056	0.9548	0.0056	0.9758	0.0054	0.9903	0.0051
Recall	0.9668	0.0002	0.9673	0.0002	0.9703	0.0037	0.9754	0.0024
AUC	0.7673	0.0099	0.7442	0.0182	0.8329	0.0029	0.8944	0.0074
Kappa	-0.0426	0.0015	-0.0377	0.0020	0.0461	0.1171	0.2766	0.1058
AUK	0.0333	0.0026	0.0266	0.0034	0.0545	0.0018	0.0782	0.0028

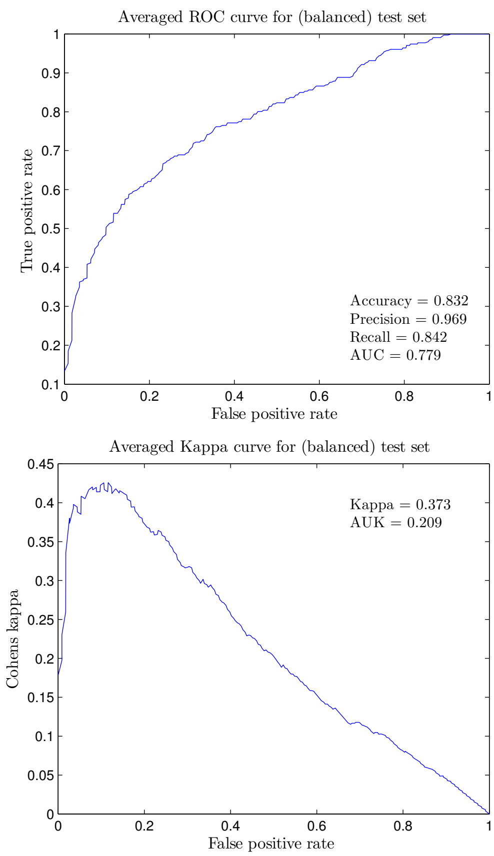

Fig. 7. Results for the logistic regression model on the (over-sampled) testing set with additional features.

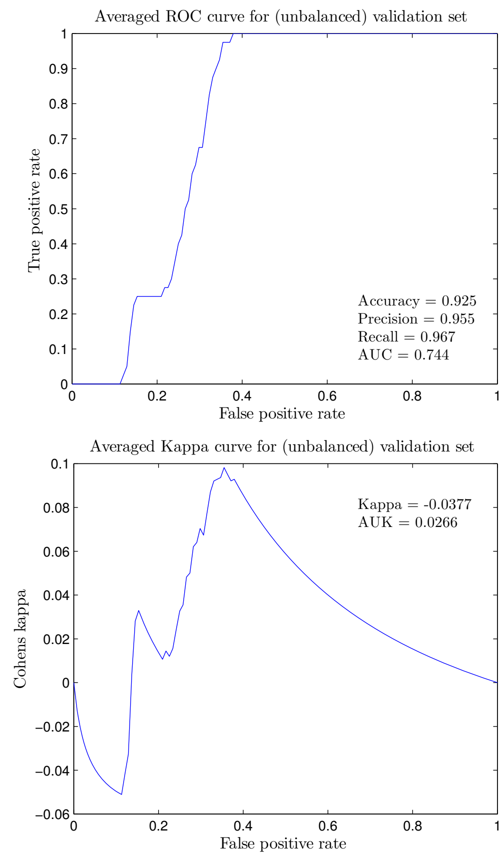

Fig. 8. Results for the logistic regression model on the (unbalanced) validation set with additional features.

For the Takagi-Sugeno Fuzzy Inference model, a difference between the two feature sets is observed, however. As in previous cases we calculated the performance measures for the two data sets. The results are shown in Fig. 9 and Fig.10, respectively. We observe that there is an increase in all the metrics for both data sets (see Table II and Table III). However, performing Student's t-test has shown that the differences were significant for the unbalanced validation data set, but they were not for the (over-sampled) testing data set. Currently, we are investigating the possible causes of this observation.

We also created models for fuzzy inference systems with different number of rules. In all cases the model built on the data set with additional features was better than a model built with the data set without those features. Furthermore, we noticed that when increasing the number of rules, the performance measures on the (over-sampled) testing set tends to increase slightly, while they tend to decrease slightly on the unbalanced validation set. We think this is related to the misclassification in the models when false positive rates are small.

Several runs indicated that FIS always performs better if it was trained on a set with additional features based on hypotension episodes. In case of logistic regression this was the case in about half the runs. Hence, it appears that

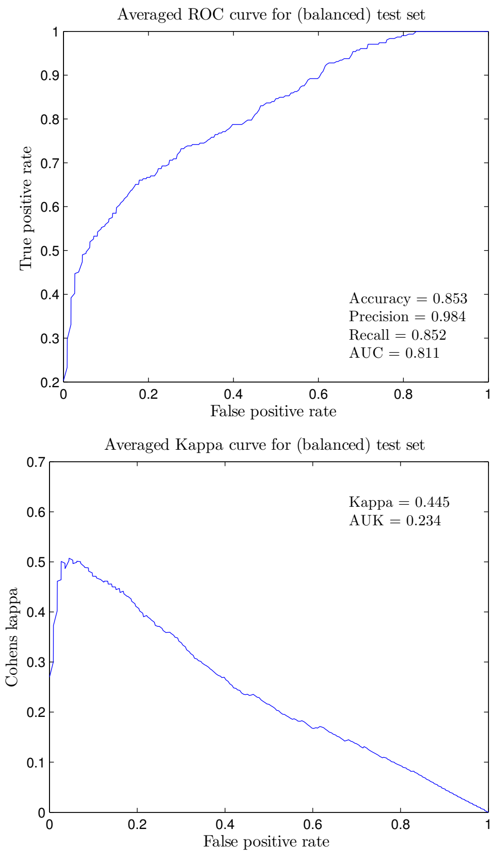

Fig. 9. Results for the FIS on the (over-sampled) test set with additional features.

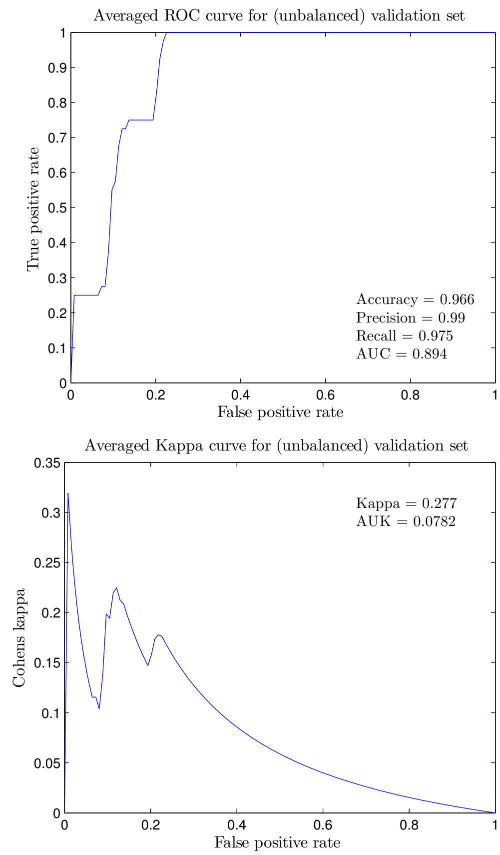

Fig. 10. Results for the FIS on the (unbalanced) validation set with additional features.

the proposed features have discriminant value in predicting leakage in sleeve gastrectomy, but the benefits are dependent on the specific modeling approach that is used.

V. Conclusions

We investigated the effect of the occurrence of hypotension episodes during the laparoscopic sleeve gastrectomy on the leakage after the surgery. We introduced features describing length and severeness of these hypotension episodes for prediction models. We tested our method on patient data from the Catharina Hospital in Eindhoven in the Netherlands by using logistic regression and Takagi–Sugeno fuzzy inference systems as modeling techniques. Results show that the new hypotension features have predictive value for leakage detection, especially for fuzzy inference systems. These results indicate that the added value of the prediction features depends also on the modeling technique selected, arguing for a wrapper approach to feature selection in modeling. In the future, we will investigate the model-dependent selection of features for this prediction problem.

From a clinical perspective, a good prediction modeling for leakage after sleeve gastrectomy can help improve the care for bariatric patients considerably. In the future, we will test these prediction models prospectively within a clinical setting.

Acknowledgements

This work is part of ongoing collaboration between the Eindhoven University of Technology and the Catharina Hospital Eindhoven for improving bariatric care. We thank L.J. De Luna Orozco, K. Pennekamp, M.P. Buise and H.H.M. Korsten for their valuable contributions to this collaboration.

References

[1] J. Dixon, “The effect of obesity on health outcomes,” *Molecular and Cellular Endocrinology*, vol. 32, p. 104108, 2010.

[2] A. Clinical and I. Committee, “Updated position statement on sleeve gastrectomy as a bariatric procedure,” *Surgery for Obesity and Related Diseases*, vol. 8, no. 3, pp. e21–e26, 2012. [Online]. Available: http://linkinghub.elsevier.com/retrieve/pii/S1550728912000354

[3] S.-h. Chang, C. R. T. Stoll, J. Song, J. E. Varela, C. J. Eagon, and G. A. Colditz, “The Effectiveness and Risks of Bariatric Surgery,” vol. 63110, no. 3, pp. 275–287, 2015. [Online]. Available: file:///C:/Users/Lenovo/Downloads/soi130085.pdf

[4] S. a. Brethauer, J. P. Hammel, and P. R. Schauer, “Systematic review of sleeve gastrectomy as staging and primary bariatric procedure,” *Surgery for Obesity and Related Diseases*, vol. 5, no. 4, pp. 469–475, 2009. [Online]. Available: http://dx.doi.org/10.1016/j.soard.2009.05.011

[5] M. Parikh, R. Issa, A. McCrillis, J. K. Saunders, A. Ude-Welcome, and M. Gagner, "Surgical strategies that may decrease leak after laparoscopic sleeve gastrectomy: a systematic review and meta-analysis of 9991 cases," *Annals of Surgery*, vol. 257, no. 2, pp. 231–237, 2013.

[6] A. R. Aurora, L. Khaitan, and A. a. Saber, "Sleeve gastrectomy and the risk of leak: A systematic analysis of 4,888 patients," *Surgical Endoscopy and Other Interventional Techniques*, vol. 26, no. 6, pp. 1509–1515, 2012.

[7] I. L. Post, P. M. Verheijen, A. Pronk, I. Siccama, and P. J. Houweling, "Intraoperative blood pressure changes as a risk factor for anastomotic leakage in colorectal surgery," *International Journal of Colorectal Diseases*, vol. 27, pp. 765–772, 2012.

[8] L. J. De Luna Orozco, "Performance of machine learning algorithms to predict anastomotic failure in bariatric surgery," Master's thesis, University of Technology Eindhoven, 2013.

[9] K. Pennekamp, "Analysis of arterial blood pressure and hypotension episodes in sleeve gastrectomy surgery," Bachelor Thesis, Eindhoven University of Technology, 2014.

[10] J. B. Bijker, W. A. van Klei, Y. Vergouwe, D. J. Eleveld, L. van Wolfswinkel, K. G. M. Moons, and C. J. Kalkman, "Intraoperative hypotension and 1-year mortality after noncardiac surgery," *Anesthesiology*, vol. 111, pp. 1217–26, 2009.

[11] S. W. Nienhuijs, L. J. de Luna, H. H. M. Korsten, U. Kaymak, and M. P. Buise, "Influence of intraoperative hypotension on leakage after sleeve gastrectomy," *Obesity Surgery*, vol. 24, no. 8, pp. 1183–1184, 2014.

[12] N. Chawla, K. Bowyer, L. Hall, and W. Kegelmeyer, "Smote: Synthetic minority over-sampling technique," *Journal of Artificial Intelligence Research*, vol. 16, pp. 321–357, 2002.

[13] I. H. Witten, E. Frank, and M. A. Hall, "Chapter 5 - credibility: Evaluating what's been learned," in *Data Mining: Practical Machine Learning Tools and Techniques*, 3rd ed. Boston: Morgan Kaufmann, 2011, pp. 147 – 187.

[14] D. C. Montgomery and G. C. Runger, *Applied Statistics and Probability for Engineers*, 5th ed. Asia: John Wiley and Sons, Inc., 2011.

[15] J. Carletta, "Assessing agreement on classification tasks: the kappa statistic," *Computational Linguistics*, vol. 22, pp. 1–6, 1996.

[16] T. Fawcett, "An introduction to ROC analysis," *Pattern Recognition Letters*, vol. 27, pp. 861–874, 2006.

[17] U. Kaymak, A. Ben-David, and R. Potharst, "The AUK: A simple alternative to the AUC," *Engineering Applications of Artificial Intelligence*, vol. 25, no. 5, pp. 1082–1089, Aug. 2012. [Online]. Available: http://dx.doi.org/10.1016/j.engappai.2012.02.012

[18] T. Takagi and M. Sugeno, "Fuzzy identification of systems and its applications to modelling and control," *IEEE Transactions on Systems, Man and Cybernetics*, vol. 15, no. 1, pp. 116–132, Jan./Feb. 1985.

[19] R. Pereira, A. Fialho, F. Cismondi, S. Vieira, J. Sousa, R. Almeida, U. Kaymak, S. Reti, M. Howell, and S. Finkelstein, "Predicting septic shock outcomes in a database with missing data using fuzzy modeling," in *Proceedings of the 2011 IEEE International Conference on Fuzzy Systems*, Taipei, Taiwan, Jun. 2011, pp. 2507–2512.

[20] F. Cismondi, A. Fialho, S. Vieira, J. Sousa, S. Reti, M. Howell, and S. Finkelstein, "New methods to processing misaligned, unevenly sampled time series containing missing data," in *2011 IEEE Symposium on Computational Intelligence and Data Mining (CIDM)*, Paris, 2011, pp. 224–231.

[21] Z. Zhang, H. Zhou, S. Liu, and P. de B. Harrington, "An application of takagi-sugeno fuzzy system to the classification of cancer patients based on elemental contents in serum samples," *Chemometrics and Intelligent Laboratory Systems*, vol. 82, no. 1-2, pp. 294 – 299, 2006.

[22] J. C. Bezdek, *Pattern Recognition with Fuzzy Objective Function Algorithms*. New York: Plenum Press, 1981.

[23] J. S. R. Jang, "ANFIS: adaptive-network-based fuzzy inference systems," *IEEE Transactions on Systems, Man and Cybernetics*, vol. 23, pp. 665–685, 1993.

[24] J. van den Berg, U. Kaymak, and R. Almeida, "Conditional density estimation using probabilistic fuzzy systems," *Fuzzy Systems, IEEE Transactions on*, vol. 21, no. 5, pp. 869–882, Oct 2013.