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Adverse Event Prediction in Patients with Left Ventricular Assist Devices

Markos G. Tsipouras, Evaggelos C. Karvounis, Alexandros T. Tzallas, Nikolaos S. Katertsidis, Yorgos Goletsis, *Member, IEEE*, Maria Frigerio, Alessandro Verde, Maria G. Trivella and Dimitrios I. Fotiadis, *Senior Member, IEEE*

***Abstract*—This work presents the Treatment Tool, which is a component of the Specialist's Decision Support Framework (SDSS) of the SensorART platform. The SensorART platform focuses on the management of heart failure (HF) patients, which are treated with implantable, left ventricular assist devices (LVADs). SDSS supports the specialists on various decisions regarding patients with LVADs including decisions on the best treatment strategy, suggestion of the most appropriate candidates for LVAD weaning, configuration of the pump speed settings, while also provides data analysis tools for new knowledge extraction. The Treatment Tool is a web-based component and its functionality includes the calculation of several acknowledged risk scores along with the adverse events appearance prediction for treatment assessment.**

I. Introduction

Heart failure (HF) is recognized as a major and escalating public health problem in industrialized countries with ageing populations [1]. Left ventricular assist devices (LVADs) which are mechanical pumps that are implanted to help the heart's weakened ventricle pump blood throughout the body, are most commonly used as a "bridge" to transplantation for those whose medical therapy has failed. LVADs can also be used as destination therapy providing long-term support in patients who are not candidates for transplant. When used as a "bridge" to transplantation or as destination therapy, the LVADs provide efficient hemodynamic support, maintain or improve other organ function, improve exercise performance and enable participation in cardiac rehabilitation. For LVADs treated patients several risk scores and prediction tools have been presented in the literature. The Heart Failure Survival Score (HFSS) has been proposed for patient selection for LVAD support based on the estimation for expected survival during the next 1 to 3 years [1]. It has been developed using statistical likelihood analysis. In the same context, Seattle Heart Failure Model (SHFM) [2] and Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure trial (REMATCH) [3] have been presented. The Interagency Registry for Mechanically Assisted Circulatory Support registry (INTERMACS) [4] has been used for patient classification in risk groups, interval analysis [5] and timing of implant prediction [6]. Also, patient classification regarding the risk of developing other diseases when undergoing LVAD implantation has been addressed with the Model for End-Stage Liver Disease (MELD) [7]. Other points also examined are the mortality risk for patients undergoing LVAD implantation [8] and screening scales for successful LVAD implantation [9-12] and high-low risk classification [13]. The selection between LVAD and BiVAD installation has been also addressed with predictive models for right ventricular failure (RVF) after LVAD implant [14], the RVF risk score (RVFRS) pre-operative tool [15] and the pre-operative right ventricular (RV) stroke work index (RVSWI) [16], which provides a quantitative measure of the ability of the RV to generate pressure. Also, HeartMate II "bridge" to transplantation (BTT) clinical trial independent predictors [17], the Right Ventricular Support Decision Tree Model (RVSDT) [18] and pre-implantation criteria [19] have been presented in the literature. Most of the aforementioned studies are based on statistical analysis techniques, while [13] and [18] employ data mining techniques.

The SensorART platform focuses on the management and remote treatment of patients suffering from HF. It provides an interoperable, extendable and VAD-independent solution, which incorporates different hardware and software components in a holistic approach, in order to improve the quality of the patients' treatment and the workflow of the specialists. The main decision support component of the SensorART project is the Specialist's Decision Support System (SDSS), which comprises from several sub-modules, mainly focusing to: (i) new knowledge discovery, (ii) statistical analysis and hypothesis testing, (iii) identification of candidate patients for VAD weaning, (iv) determination of an optimal VAD pump speed, (v) detection suction events of the rotary blood pumps (in the framework of speed selection), and (vi) risk scores calculation for adverse events prediction in relation to alternative treatments prediction. The Treatment Tool of the SDSS materializes the later functionality.

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M. G. Tsipouras, E. C. Karvounis, A. T. Tzallas and N. S. Katertsidis are with the Biomedical Research Institute-FORTH, GR 45110, Ioannina, Greece (e-mail: markos@cs.uoi.gr, ekarvuni@cc.uoi.gr, atzallas@cc.uoi.gr, nkatertz@cc.uoi.gr, goletsis@cc.uoi.gr).

Y. Goletsis is with the Biomedical Research Institute-FORTH, GR 45110, Ioannina, Greece and with the Department of Economics, University of Ioannina, GR45110 Ioannina, (e-mail: goletsis@cc.uoi.gr).

M. Frigerio and A. Verde are with Cardiology 2 - Heart Failure and Transplantation Division, "A. De Gasperis" Cardiothoracic & vascular Department, Niguarda Ca' Granda Hospital, Milan (e-mail: MARIA.FRIGERIO@OspedaleNiguarda.it, alessandro.verde@gmail.com).

M.G. Trivella is with the Istituto di Fisiologia Clinica-CNR, Pisa, Italy (e-mail: trivella@ifc.cnr.it).

D.I. Fotiadis is with Biomedical Research Institute-FORTH, GR 45110, Ioannina, Greece and with the Unit of Medical Technology and Intelligent Information Systems, Dept. of Materials Science and Engineering, University of Ioannina, GR 45110 Ioannina, Greece (tel.: +30 26510 08803, fax: +30 26510 07092; e-mail: fotiadis@cc.uoi.gr)

II. Materials and Methods

A. Design

The Treatment Tool is a web-based component and consists of the client-side and the server-side subcomponents that implement the different risk indices/adverse event models and their evaluation mechanism. The Treatment Tool provides two functionalities: (i) known risk scores calculation, and (ii) treatment prediction based on risk for adverse events appearance.

B. Risk Scores Calculation

Several known scores of survival are incorporated in the SDSS to allow rapid decisions and to foresee possible complications after VAD implant. As depicted in the introduction, risk scores are calculated for similar and partially overlapped - but not identical - objectives:

- to predict the expected survival / the risk of death on medical therapy
- to predict the expected survival / the risk of death after LVAD implantation
- to predict the probability of specific complications (e.g. right ventricular failure) after LVAD implantation.

Unfortunately, some risk factors for death without operation are also associated with worse postoperative survival and/or higher probability of complications, making difficult to define the risk/benefit profile for individual patients. The following risk scores are included in the Treatment Tool: the HFSS, the SHFM, the MELD and the RVFRS. Through the main follow-up data, the Specialist accesses the Treatment Tool, and selects one of the available functionalities e.g. HFSS calculation. He/she is then presented with the corresponding form, where he/she can fill-in the required parameters and values and get the respective estimated score.

C. Treatment Prediction Based on Adverse Events Appearance

This modality assesses the risk of adverse events in the case of LVAD implantation. It has been developed by applying machine learning techniques in an annotated dataset. The dataset includes data from 49 patients, each recording having the same variables, presented in Table I.

The re-hospitalizations for all patients for the 1st year and follow-up data have been used to determine the occurrence of adverse events: among 49 patients treated with VADs, 35 had no relevant adverse events, 3 had bleeding episodes and 11 died. Being common, not rarely recurrent, and most often benign, infections of the entry site of the driveline were not considered as relevant adverse events. The dataset included several missing values (Fig. 1) thus replacement of missing values has been applied using the 3-Nearest Neighbors technique. Also, the number of the prototypes per category is unbalanced, thus the resampling from the normal distribution of the minority class procedure has been employed. In addition, a feature selection was applied based on chi-squared statistics with respect to the class and exhaustive search, in order to select the most informative features for this problem. Feature selection resulting to the subset of features presented in Table II.

TABLE I. Features in the Dataset

Feature	mean ± std	Feature	mean ± std
Age	54.16 ± 10.65	reversible PH	1 (median)
INTERMACS profile	2 (median)	HR	84.88 ± 11.09
		PA	98.96 ± 13
Platelets	267.04 ± 119.5	INR	1.46 ± 0.69
Hb	12.38 ± 1.5	bilirubine	1.28 ± 1.17
Hct	37.76 ± 4.84	creatinine	1.18 ± 0.44
WBC	9.66 ± 4.86	urea	267.04 ± 119.5
RAP	7.58 ± 5.33	Na+	138.42 ± 7.98
PAP-max	51.76 ± 18.18	MELD	10.72 ± 5.62
PAP-min	23.14 ± 8.66	MELD UNOS	12.91 ± 4.18
PAP-mean	35.5 ± 10.75	MELD U+Age	62.85 ± 12.56
PCW	25.71 ± 9.32	AST	49.9 ± 96.45
Cardiac Index	1.78 ± 0.47	inotropes	0.63 ± 0.87

Figure 1. Missing values (%) in the dataset.

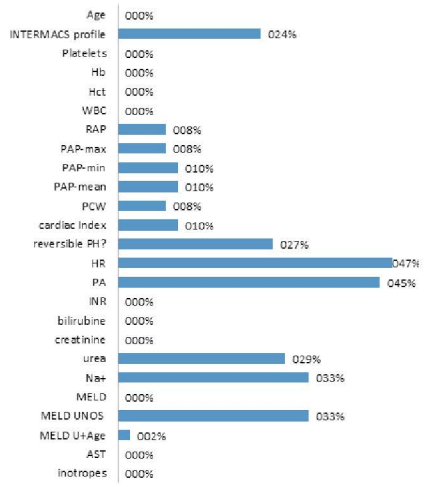


TABLE II. Features Selected from the Dataset

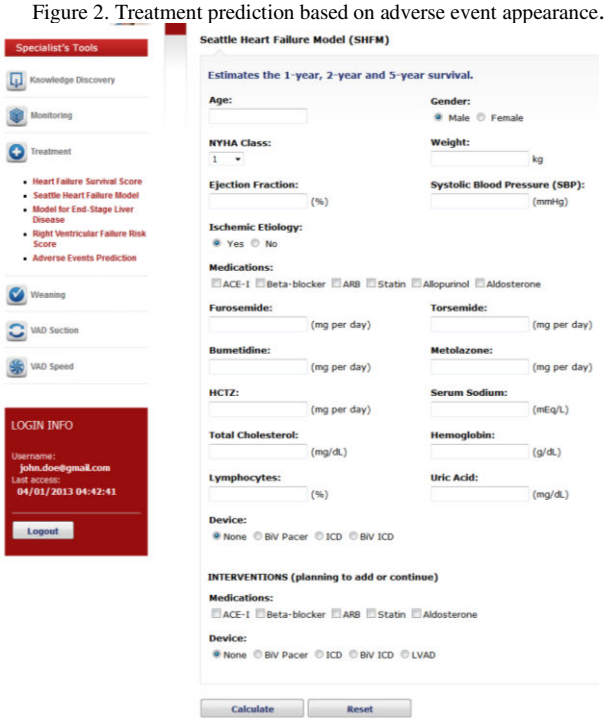
Feature	mean ± std
Hb	11.93 ± 1.54
Hct	36.58 ± 4.61
RAP	8.92 ± 5.68
cardiac Index	1.62 ± 0.39
INR	1.25 ± 0.27
AST	44.75 ± 56.19

To assess the appearance of adverse events, five known classification methodologies have been tested:

- Naïve Bayes classifier (NB)
- k-nearest-neighbor (kNN), with k=3
- Decision trees (DT), using the C4.5 algorithm
- Random forests (RF), with 10 trees
- Multilayer perceptron (MLP) neural networks, with 1 hidden layer
- Support Vector Machines (SVMs) with grid search.

Based on the obtained results (presented in the next section) and on the complexity of the classifiers the DT model has been selected (as an initial approach) for the Treatment Tool. The implementation of the treatment prediction based on e.g. SHFM treatment risk score is presented in Fig. 2.

Figure 2. Treatment prediction based on adverse event appearance.

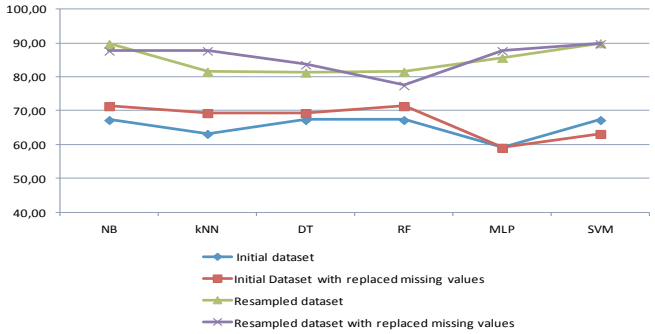


III. Results

Evaluation was performed for (i) the initial dataset (init), (ii) the initial dataset with replaced missing values (init_rmv), (iii) the resampled dataset (resmp) and (iv) resampled dataset with replaced missing values (resamp_rmv). The respective confusion matrices were obtained, while the metrics of classification accuracy (acc), average sensitivity for all classes (sens) and average positive predictive value (PPV) for all classed are calculated.

All results are presented in Tables III (a) to (d), while a graphic representation of the classification accuracy for all classification techniques and different datasets is illustrated in Fig. 3.

Figure 3. Overall classification accuracy results.



IV. Discussion & Conclusions

In this paper the Treatment Tool of the SDSS of the SensorART platform has been presented. The Treatment tool includes both known risk scores that have been presented in the literature, along with an adverse event prediction model that have been developed using a set of 49 patients.

The medical experts in the SensorART project have suggested the selected risk scores that have been included in the Treatment tool, as the most helpful to the clinical practice. Several additional risk scores proposed in the literature are developed in order to included in the platform so as to offer a complete set of medical tools for decision support.

Currently the model for adverse events prediction is based on DTs. This selection was made using the obtained results, were the DTs achieved very good results, compared to the

TABLE III. Classification Accuracy Results for all Datasets and Classifiers

(a)	Initial dataset		
	Sens (%)	*PPV (%)*	*Acc (%)*
NB	37.66	38.68	67.35
kNN	35.76	43.93	63.27
DT	37.66	37.50	67.35
RF	35.58	35.14	67.35
MLP	44.01	48.87	59.18
SVM	51.98	55.96	67.35

(b)	Initial dataset with replaced missing values		
	Sens (%)	*PPV (%)*	*Acc (%)*
NB	39.57	41.47	71.43
kNN	42.77	44.64	69.39
DT	52.93	50.32	69.39
RF	41.65	41.87	71.43
MLP	33.85	32.41	59.18
SVM	50.07	53.82	63.27

(c)	Resampled dataset		
	Sens (%)	*PPV (%)*	*Acc (%)*
NB	93.16	89.43	89.80
kNN	87.27	70.28	81.63
DT	87.27	67.85	81.36
RF	89.35	83.99	81.63
MLP	89.18	86.01	85.71
SVM	91.16	89.76	90.00

(d)	Resampled dataset with replaced missing values		
	Sens (%)	*PPV (%)*	*Acc (%)*
NB	88.05	82.14	87.76
kNN	90.13	77.98	87.76
DT	86.15	73.47	83.67
RF	85.37	66.67	77.55
MLP	90.13	87.72	87.76
SVM	81.82	89.71	89.80

TABLE IV. DATA MINING APPROACHES

Authors	Medical problem	Missing data management	Resampling	Classification	Results (acc)
Wang et al. [13]	90-day mortality	mean, median, kNN (k = 1, 3, 5, 7, 10, 15)		DT SVM BTN	61.20% 62.34% 57.54%
Wang et al. [18]	LVAD vs LVAD/RVAD	mean, median, kNN (k = 1, 3, 5, 7, 10, 15, 20)	SMOTE	DT	87 (AUC)%
This work	risk of adverse events appearance (1 year)	kNN k = 3	resampling from the normal distribution of the minority class	NB kNN (k=3) DT RF MLP SVM	89.80% 87.76% 83.67% 81.63% 85.71% 90%

AUC: area under curve, BTN: Bayesian Tree-Augmented Network

other techniques included in the study, and they present relatively low complexity, compared to MLP and SVM. However, the SensorART platform is populated day-by-day with new data; when larger and more complex datasets will be involved in the evaluation, this selection will be re-evaluated based on a wider dataset and the new results. Thus the classification algorithm that will be finally integrated into the SensorART platform is subject to research.

The other risk scores presented in the literature are mainly based on classical statistical techniques for analysis. In this study, mainly data mining techniques have been involved. The other two approaches proposed in the literature that involve data mining are the works by Wang et al. [13,18]. In [13] the authors are trying to assess the risk for 90-day mortality. They apply several missing data management techniques (mean, median and kNN with k = 1, 3, 5, 7, 10 and 15) and several classification techniques including DTs, SVMs and a Bayesian tree-augmented network. In [18] the LVAD vs. LVAD/RVAD decision is assessed. Again, missing data management includes mean, median and kNN with k = 1, 3, 5, 7, 10, 15 and 20, while a resampling technique (SMOTE) has been employed. In addition feature selection has been applied based on feature ranging with chi-square statistics, while classification is based on DTs. In Table III all approaches that have been presented in the literature employing data mining techniques for analysis, are presented. Although a direct comparison is not feasible, since different datasets have been involved in each case, the proposed method compares well in terms of accuracy and therefore can be considered as a good candidate for supporting physicians in treatment related decisions.

REFERENCES

[1] K. D. Aaronson, J. S. Schwartz, T. -M. Chen, K. -L. Wong, J. E. Goin, D. M. Mancini, "Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation," *Circulation*, vol. 95, pp. 2660-7, 1997.

[2] W.C. Levy et al., "The Seattle heart failure model: prediction of survival in heart failure," *Circulation*, vol. 113, pp. 1424-33, 2006.

[3] W. C. Levy et al, "Can the Seattle heart failure model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy?," *J Heart Lung Transplant*, vol. 28, pp. 231-6, 2009.

[4] J. K. Kirklin, et al., "Second INTERMACS annual report: More than 1,000 primary left ventricular assist device implants," *J Heart Lung Transplant*, vol. 29, pp. 1-10, 2010.

[5] W. I. Holman et al., "INTERMACS: interval analysis of registry data", *J Am Coll Surg*, vol. 208, pp. 755-61; 2009.

[6] L. W. Stevenson et al., "INTERMACS profiles of advanced heart failure: the current picture," *J Heart Lung Transplant*, vol. 28, pp. 535-41, 2009.

[7] J. C. Matthews, T. M. Koelling, F. D. Pagani, and K. D. Aaronson, "Model for End-Stage Liver Disease Score Predicts Left Ventricular Assist Device Operative Transfusion Requirements, Morbidity, and Mortality," *Circulation*, vol. 121, pp. 214-220, 2010.

[8] D. J. Farrar, "Preoperative predictors of survival in patients with Thoratec ventricular assist devices as a bridge to heart transplantation. Thoratec Ventricular Assist Device Principal Investigators," *J Heart Lung Transplant*, vol. 13, pp. 93-100, 1994.

[9] C. O. Oz et al., "Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices," *Circulation*, vol. 92, pp. 69-73, 1994.

[10] V. Rao et al., "Revised screening scale to predict survival after insertion of a left ventricular assist device," *J Thorac Cardiovasc Surg*, vol. 125, pp. 855-62, 2003.

[11] C. Y. Lin et al., "Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation," *Ann Thorac Surg*, vol. 84, pp. 1256-62, 2007.

[12] K. Lietz et al., "Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection," *Circulation*, vol. 116, pp. 497-505, 2007.

[13] Y. Wang, C. P. Rosé, A. Ferreira, D. M. McNamara, R. L. Kormos, and J. F. Antaki, "A Classification Approach for Risk Prognosis of Patients on Mechanical Ventricular Assistance," in *Proc Int Conf Mach Learn Appl.*, pp. 293–298, 2010.

[14] J. R. Fitzpatrick et al., "Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support," *J Heart Lung Transplant*, vol. 27, pp. 1286-92, 2008.

[15] J. C. Matthews, T. M. Koelling, F. D. Pagani, and K. D. Aaronson, "The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates," *J Am Coll Cardiol*, vol. 51, pp. 2163-72, 2008.

[16] Y. Ochiai et al., "Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients," *Circulation*, vol. 106, pp. I198-I202, 2012.

[17] R. L. Kormos et al., "Right ventricular failure in patients with the HeartMate II continuous flow left ventricular assist device: incidence, risk factors, and impact on outcomes," *J Thorac Cardiovasc Surg*, vol. 139, pp. 1316-24, 2010.

[18] Y. Wang, M. Simon, P. Bonde, B. U. Harris, J. J. Teuteberg, R. L. Kormos, and J. F. Antaki, "Prognosis of Right Ventricular Failure in Patients with Left Ventricular Assist Device based on Decision Tree with SMOTE," *IEEE Trans Info Tech Biomed*, vol. 16, pp. 293–298, 2012.

[19] M. S. Slaughter et al., "Clinical management of continuous-flow left ventricular assist devices in advanced heart failure," *J Heart Lung Transplant*, vol.29, pp. S1-S39, 2010.