Série dos Seminários de Acompanhamento à Pesquisa

DEI
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Predicting the Acquisition of Resistant Pathogens in ICUs using Machine Learning Techniques

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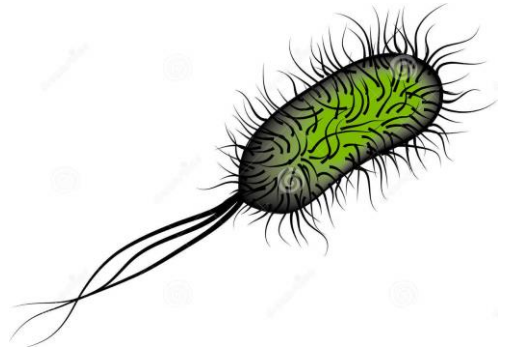
Introduction

- Infections by antibiotic-resistant bacteria are one of the most significant current threats to global health;
- WHO: Gram-negative pathogens resistant to carbapenems are a critical priority;
- Increased attributable morbidity, mortality, hospitalization time, and economic costs;
- Mortality 1.78 times higher in patients with MDR-GNB infections;



Objectives

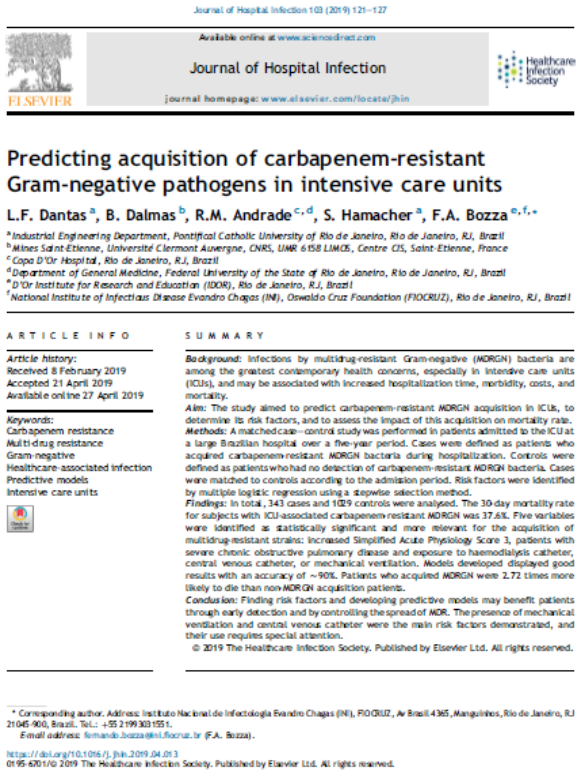
Main

To develop models to predict CR-GNB acquisition in ICUs using machine-learning techniques.

Specific Objectives

1) To predict CR-GNB acquisition in ICUs, determining its risk factors, and assessing the impact on mortality rate using the logistic regression technique.

Paper:https://www.journalofhospitalinfection.com/article/S0195-6701(19)30182-3/fulltext



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Predicting acquisition of carbapenem-resistant Gram-negative pathogens in intensive care units

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SUMMARY

Background: Infections by multidrug-resistant Gram-negative (MDRGN) bacteria are among the greatest contemporary health concerns, especially in intensive care units (ICUs), and may be associated with increased hospitalization time, morbidity, costs, and mortality.
Aim: The study aimed to predict carbapenem-resistant MDRGN acquisition in ICUs, to determine its risk factors, and to assess the impact of this acquisition on mortality rate.
Methods: A matched case–control study was performed in patients admitted to the ICU at a large Brazilian hospital over a five-year period. Cases were defined as patients who acquired carbapenem-resistant MDRGN bacteria during hospitalization. Controls were defined as patients who had no detection of carbapenem-resistant MDRGN bacteria. Cases were matched to controls according to the admission period. Risk factors were identified by multiple logistic regression using a stepwise selection method.
Findings: In total, 343 cases and 1029 controls were analysed. The 30-day mortality rate for subjects with ICU-associated carbapenem-resistant MDRGN was 37.6%. Five variables were identified as statistically significant and more relevant for the acquisition of multidrug-resistant strains: increased Simplified Acute Physiology Score 3, patients with severe chronic obstructive pulmonary disease and exposure to haemodialysis catheter, central venous catheter, or mechanical ventilation. Models developed displayed good results with an accuracy of ~90%. Patients who acquired MDRGN were 2.72 times more likely to die than non-MDRGN acquisition patients.
Conclusion: Finding risk factors and developing predictive models may benefit patients through early detection and by controlling the spread of MDR. The presence of mechanical ventilation and central venous catheter were the main risk factors demonstrated, and their use requires special attention.

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Objectives

Main

To develop models to predict CR-GNB acquisition in ICUs using machine-learning techniques.

Specific Objectives

2) Screening model to detects ICU patients who need to be tested;

3) Evaluating different machine learning and imbalanced learning method;

4) Developing a risk model that estimates ICU patients' probability of acquiring CR-GNB;

Differences between the models

Model	Screening	Acquisition risk
Type	Discrimination/Classification	Prediction
Study Population	All Screenings Tests	Screening Tests and Clinical Exams
Unit of Analysis	Test	Patient
Main Objective	To detect those who do NOT need testing	To find the probability of each patient to acquire the bacteria
Sampling method	Different Balancing Strategies	Matched Case-control Study
Hyperparameter Tuning Metric	AUC	Brier score
Evaluation Metric	MCC and NPV	Brier score
Interpretation	Error analysis (confusion matrix)	Calibration Belt
Comparison of the techniques' performances	Yes	No
Computational Time Analysis	Yes	No
Analysis of the difference between hospitals	No	Yes
Importance Factors	No	Yes
Association Rules Mining	No	Yes

Methods

Study overview

- Hospitalized patients in 24 ICUs of five hospitals at a sizeable Brazilian network hospitals;

Hospital	# ICUs	# ICU Beds	# Annual ICU admission
A	1	~10	~600
B	2	~26	~1400
C	5	~52	~4500
D	9	~140	~5700
E	7	~92	~5300

- The experiments were performed on an Intel® Core ™ i7 processor with 16GB of RAM and R 4.0.2 software;
- We used the CARET framework, imbalanced-learn packages, and others;
- We adapted all the functions of balancing strategies in CARET;

Methods

Database settings

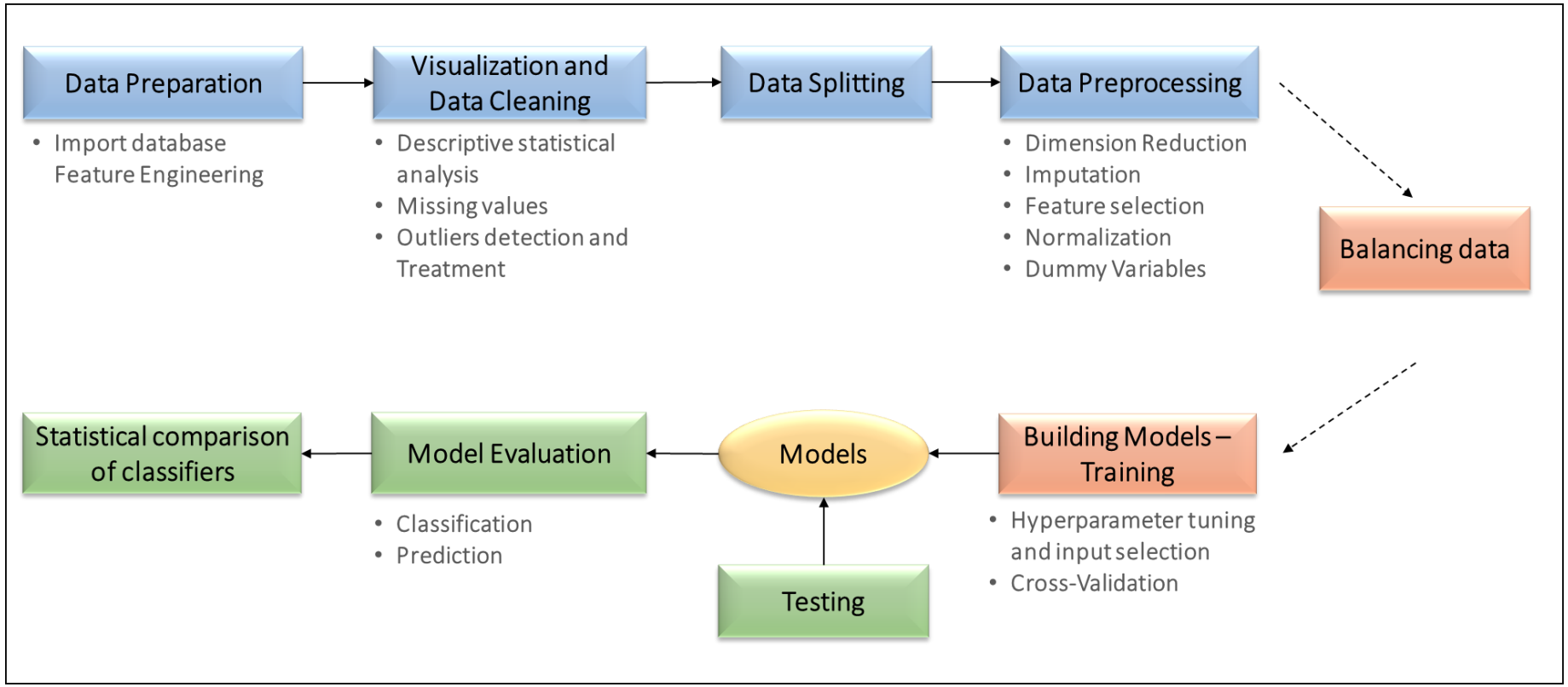
- Epimed Monitor System®
  - Patient, ICU and hospital information;
  - Indexes (such as SAPS3 and Charlson);
  - Presence of comorbidities;
  - Use of the invasive devices during hospitalization;
  - Reasons for ICU admission;
- Business Intelligence (BI) System
  - Antibiotic data
- REAL system
  - Microbiology data → Laboratory test results (positive/negative).

We included 44 new input attributes.

Methods

Conducting a Machine learning analysis

- Our analysis adds to the current studies in four respects: machine learning techniques, balancing strategies, feature selection, and performance evaluation;



Methods

- Machine Learning Techniques and Balancing strategies

Method	Algorithm
LINEAR CLASSIFICATION MODELS	
Logistic Regression	glm
Logistic Regression with regularization	glmnet
Linear Discriminant Analysis (LDA)	lda
Nearest Shrunken Centroids (NSC)	pam
Support Vector Machine (SVM) - Linear	svmLinear
NONLINEAR CLASSIFICATION MODELS	
Neural Network	nnet
Support Vector Machine (SVM) - Radial	svmRadial
k-Nearest Neighbors (kNN)	kNN
Naive Bayes	naive_bayes
CLASSIFICATION TREES	
Decision Tree C45	J48
Decision Tree CART	rpart
Decision Tree C50	C5.0
Random Forest (RF)	rf
Gradient Boosting Machines (GBM)	gbm
Bagging	treebag
AdaBoost	AdaBoost.M1

Balancing approaches
SAMPLING
Random downsampling (or undersampling)
Random upsampling (or oversampling)
SMOTE
DATA CLEANING TECHNIQUES
Tomek Links
Neighbourhood Cleaning Rule (NCL)
One-sided selection (OSS)
SMOTE + Tomek
SMOTE + NCL
SMOTE + OSS
ENSEMBLE-BASED METHODS
SMOTEBoost
RUSBoost
SMOTEBagging
UnderBagging

Differences between the models

Model	Screening	
Type	Discrimination/Classification	Prediction
Study Population	All Screenings Tests	Screening Tests and Clinical Exams
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Main Objective	To detect those who do NOT need testing	To find the probability of each patient to acquire the bacteria
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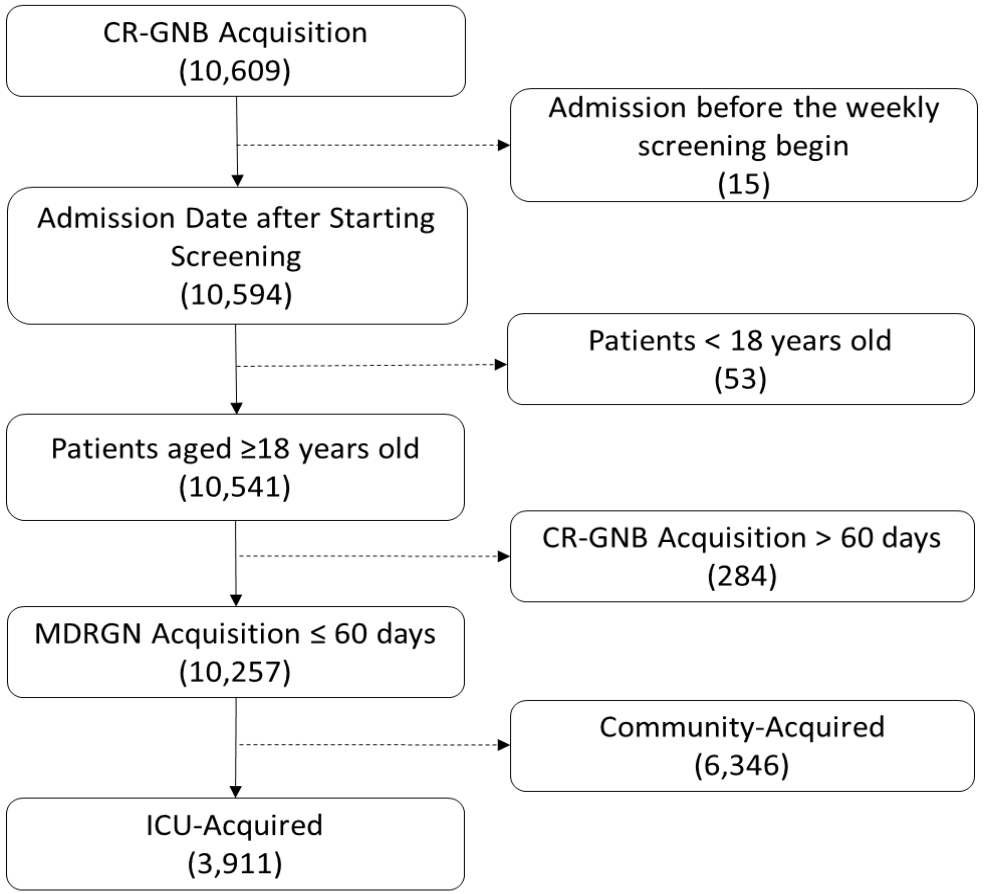
Importance Factors	No	Yes
Association Rules Mining	No	Yes

Screening Model

Setting and Study population

Inclusion criteria:

- Tests realized between 48h and 60days after patient admission and made in adult ICUs.
- Testing in patients with admission date after May 8th, 2017 until August 31st, 2019;
- Patients aged ≥18 years old;
- Total: 3,911 tests
  - Positive = 394
  - Negative = 3,517



Screening Model

Descriptive analysis

– Patients more likely to be colonized:

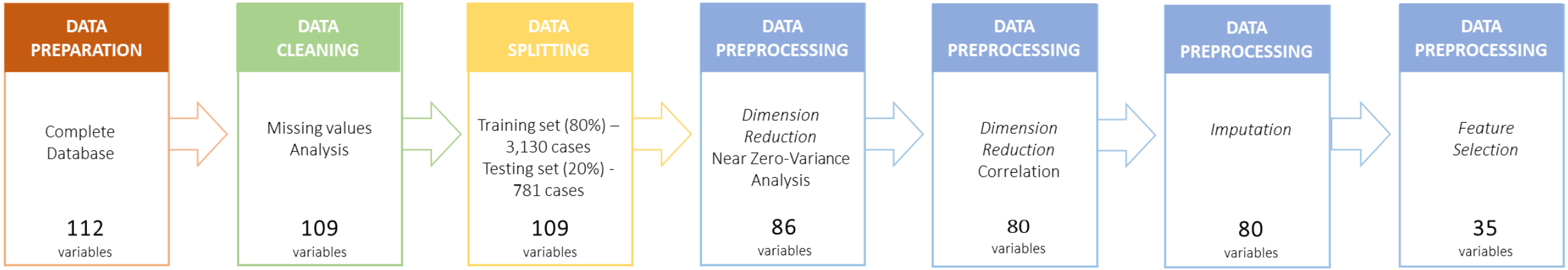
- High length of stay in hospital or ICU;
- Higher severity indices;
- Antibiotics use;
- Invasive devices between 24 hours to 30 days before the test;
- Prolonged use time of mechanical ventilation and catheters;
- Higher duration that a procedure is used between one test and another and the number of times they were changed;
- Admitted from sepsis/infection or neurological disease and by the operation room or other ICU from the hospital;

Screening Model

Setting and Study population

Hospital	#Screening Tests	#Positive Tests	#Negative Tests	% Positive Tests
A	310	60	250	19.4%
B	806	57	749	7.1%
C	1081	81	1000	7.5%
D	1714	196	1518	11.4%
All	3911	394	3517	**11.3%**

Screening Model



Screening Model

Data Preprocessing

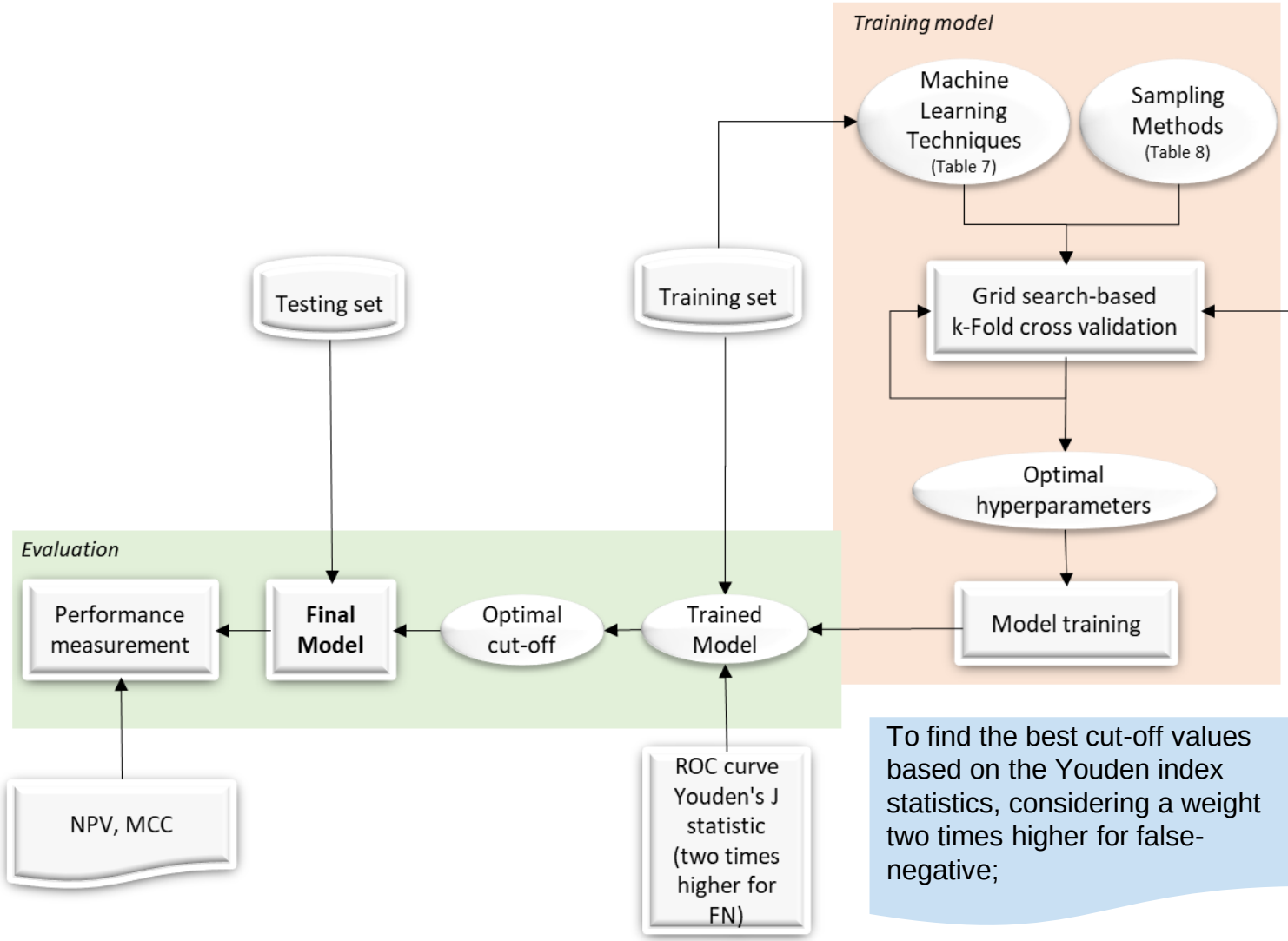
Feature Selection

	Mean AUC values				AR	Number of variables
	C45	SVM Radial	KNN	LR		
Recursive Feature Elimination with random forest (RF-RFE)	0.632	0.690	0.642	0.713	**1.25**	35
Selection by Filter (SBF)	0.624	0.674	0.625	0.709	**2.75**	42
Class Decomposition with filter (D.SBF)	0.568	0.658	0.641	0.702	**3.75**	76
Class Decomposition with random forest (D.RF)	0.607	0.687	0.658	0.708	**2.25**	24
Friedman test (p-value)			**0.007**			

- We proposed an approach combining feature selection and cluster techniques: D.RF.
  - The second best when comparing AUC;
  - The best one to discriminate the positive classes comparing the Sensitivity;

Screening Model

Building model – Training



No measure simultaneously combines the threshold for classification and the estimated probability.

After proposing the final models with the best hyperparameters, we evaluate the performance using the test set.

We used a tuned grid search to determine sets of hyperparameters that optimize each model fit → 10-fold cross-validation;

The model that maximize prediction based on AUC are stored and used to the final training model;

To find the best cut-off values based on the Youden index statistics, considering a weight two times higher for false-negative;

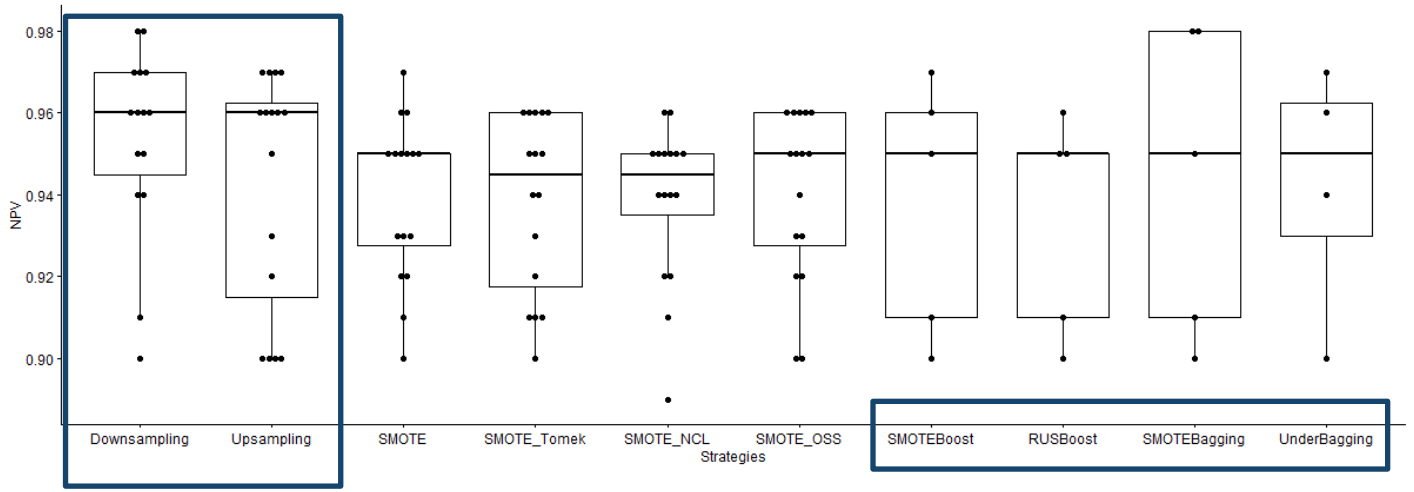
Screening Model

✓ **Evaluating different machine learning and imbalanced learning method**

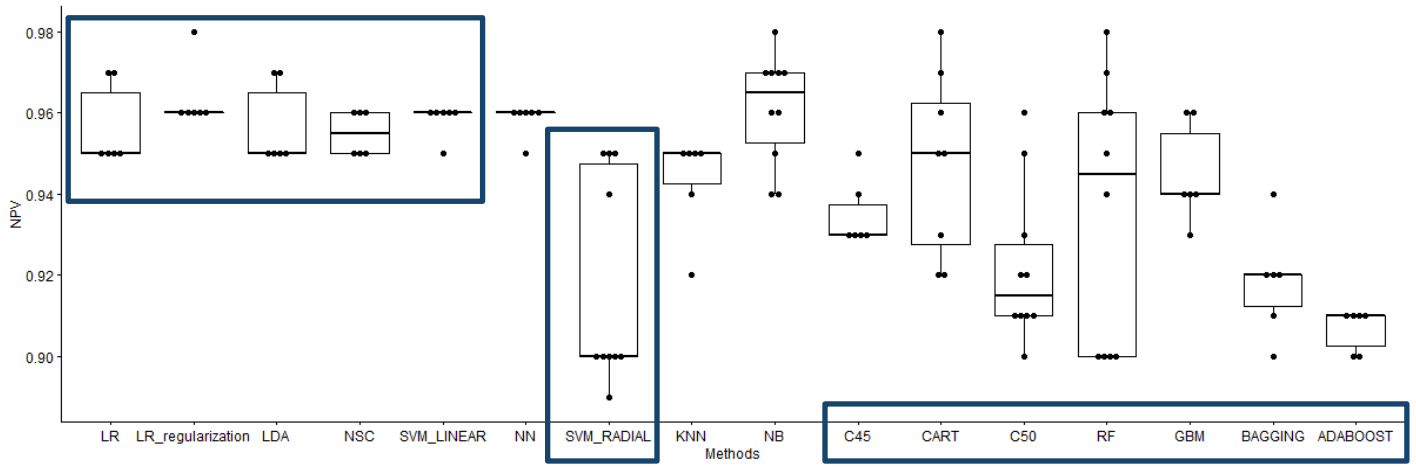
NPV

Friedman chi-squared → p-value < 0.001

Boxplots representing the NPV of each method (points) for all strategies.



Boxplots representing the NPV of each strategy (points) for all methods.



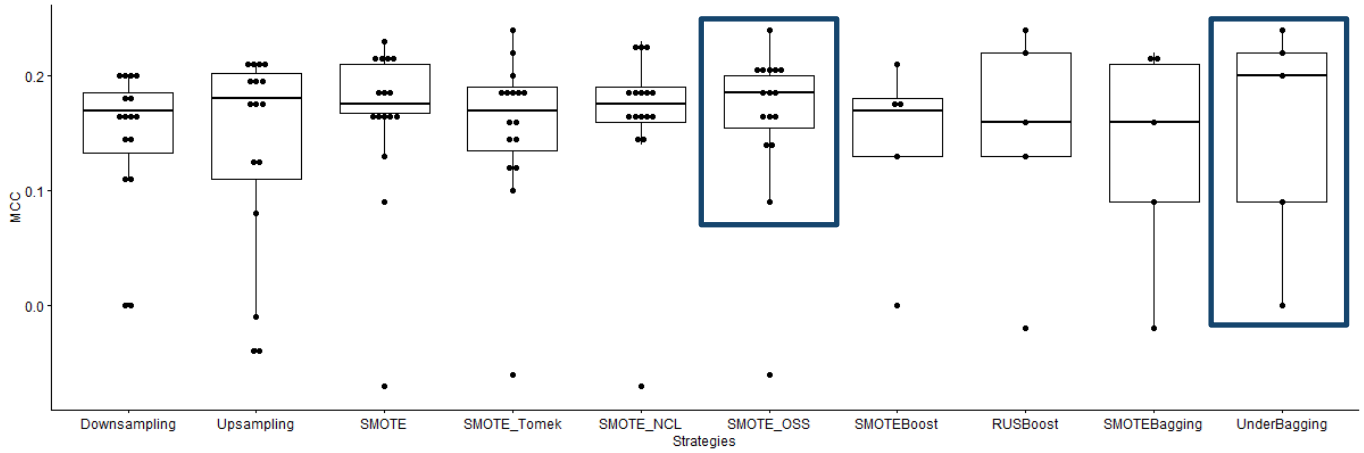
Screening Model

✓ **Evaluating different machine learning and imbalanced learning method**

MCC

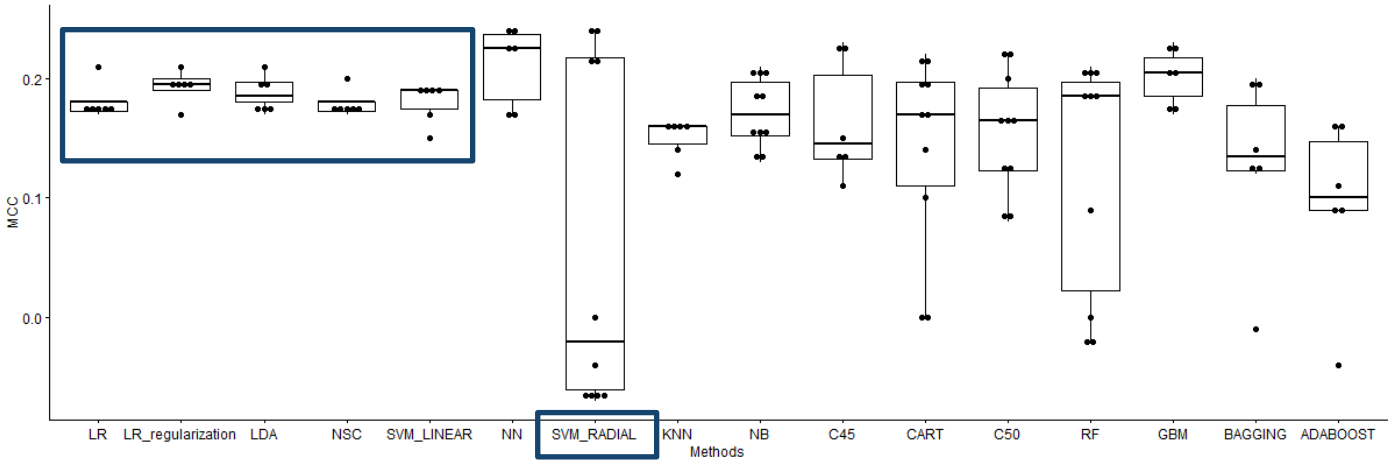
Friedman chi-squared → p-value < 0.001

Boxplots representing the MCCs of each method (points) for all strategies



There is no generic rule to choose a single best method or strategy. The choice will depend on each problem, database, and evaluation metric used.

Boxplots representing the MCCs of each strategy (points) for all methods



Screening Model

✓ **Computational Time**

Timing Final Model

- The sampling strategies have the lowest medians, followed by data cleaning strategies;
- Tree-based strategies take longer to build the final model;
- The linear models are more efficient, followed by decision trees;
- The SVM Radial and Adaboost are the slowest;

Strategies	Timing Everything (min) Median	Timing Final Model (min) Median
Downsampling	24.1	0.1
Upsampling	40.9	0.5
OSS	43.3	0.9
SMOTE	67.0	0.4
Tomek	74.4	0.5
UnderBagging	75.3	2.4
NCL	121.4	1.3
SMOTE_Tomek	125.1	0.7
SMOTE_OSS	135.2	0.9
SMOTE_NCL	157.6	1.3
RUSBoost	1001.9	6.5
SMOTEBoost	1402.7	9.3
SMOTEBagging	1474.3	10.3

Methods	Timing Everything (min) Median	Timing Final Model (min) Median
LDA	6.1	0.5
LR	6.4	0.5
NSC	6.5	0.5
CART	7.6	0.6
BAGGING	9.8	0.9
C50	39.2	1.6
KNN	44.8	0.5
LR_regularization	51.1	0.6
SVM_LINEAR	180.8	4.2
RF	292.4	2.0
NN	297.0	1.0
NB	319.8	0.8
C45	413.5	0.6
ADABOOST	451.8	11.8
GBM	815.5	2.4
SVM_RADIAL	1562.2	3.6

Screening Model

✓ Model Analysis

– We analyze each false-negative case found in the confusion matrices of the best-classifiers using the 781 (78 positives and 703 negatives) data test;

CONSERVATIVE MODEL (BY NPV) - NB, RF, and LR regularized

RF (downsampling)				
Sens	Spec	PPV	NPV	AUC
0.92	0.39	0.14	0.98	0.75

		Reference	
		Pos	Neg
Predicted	Pos	72	429
	Neg	**6**	**274**

✓ Reduce 280 tests (36%), but 6 patients non-isolated;

MODERATE MODEL (BY MCC) - NN and SVM Radial

NN (SMOTE+Tomek)				
Sens	Spec	PPV	NPV	MCC
0.76	0.64	0.19	0.96	0.24

		Reference	
		Pos	Neg
Predicted	Pos	59	251
	Neg	**19**	**452**

✓ Reduce 471 tests (64%), but 19 patients non-isolated;

Differences between the models

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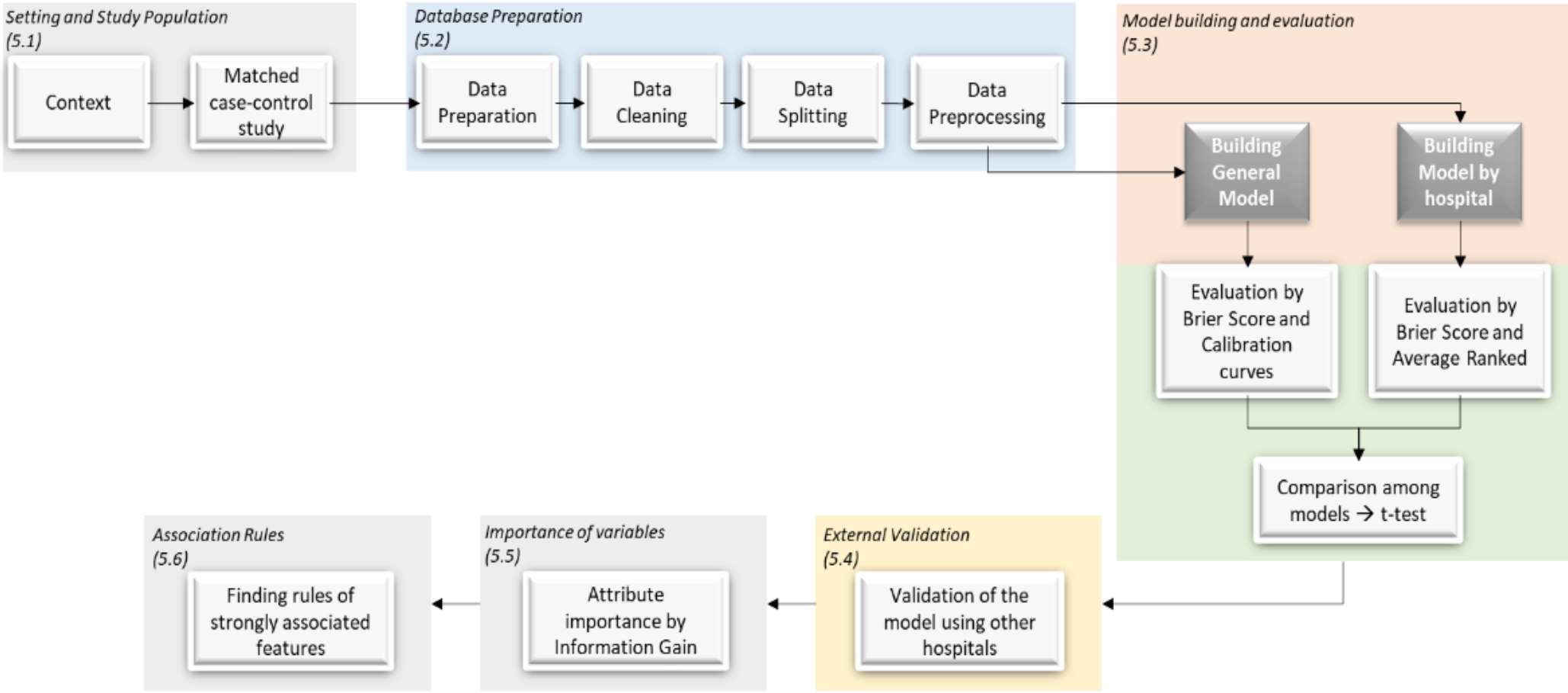
Association Rules Mining	No	Yes

Risk Model for the acquisition of CR-GNB



Risk Model for the acquisition of CR-GNB

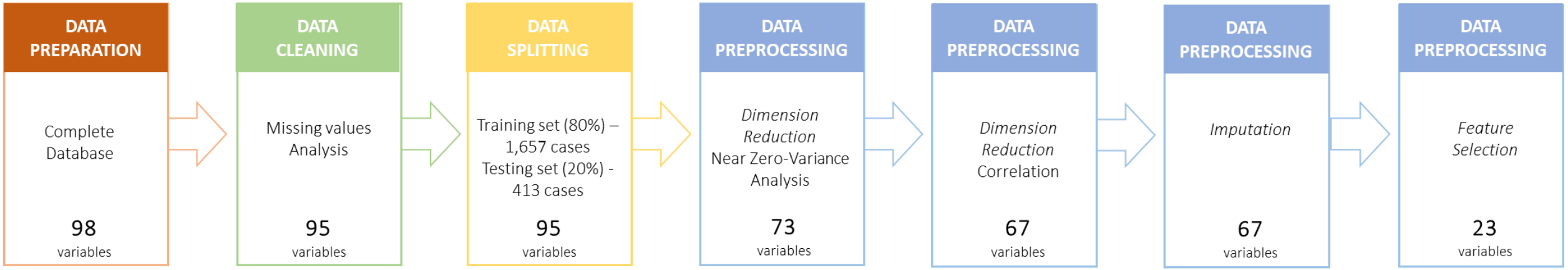
✓ **Setting and study population**

Hospital	# Tests	# Negative Tests	# Positive Tests	# Patients
A	404	341	63	214
B	1,039	971	68	469
C	1,540	1,452	88	611
D	3,849	3,616	233	1,658
E	1,157	1,082	75	652
All	7,989	7,462	527	3,604

- Unit of analysis → Patient;
- A matched case-control design by the hospital and admission date (3:1);

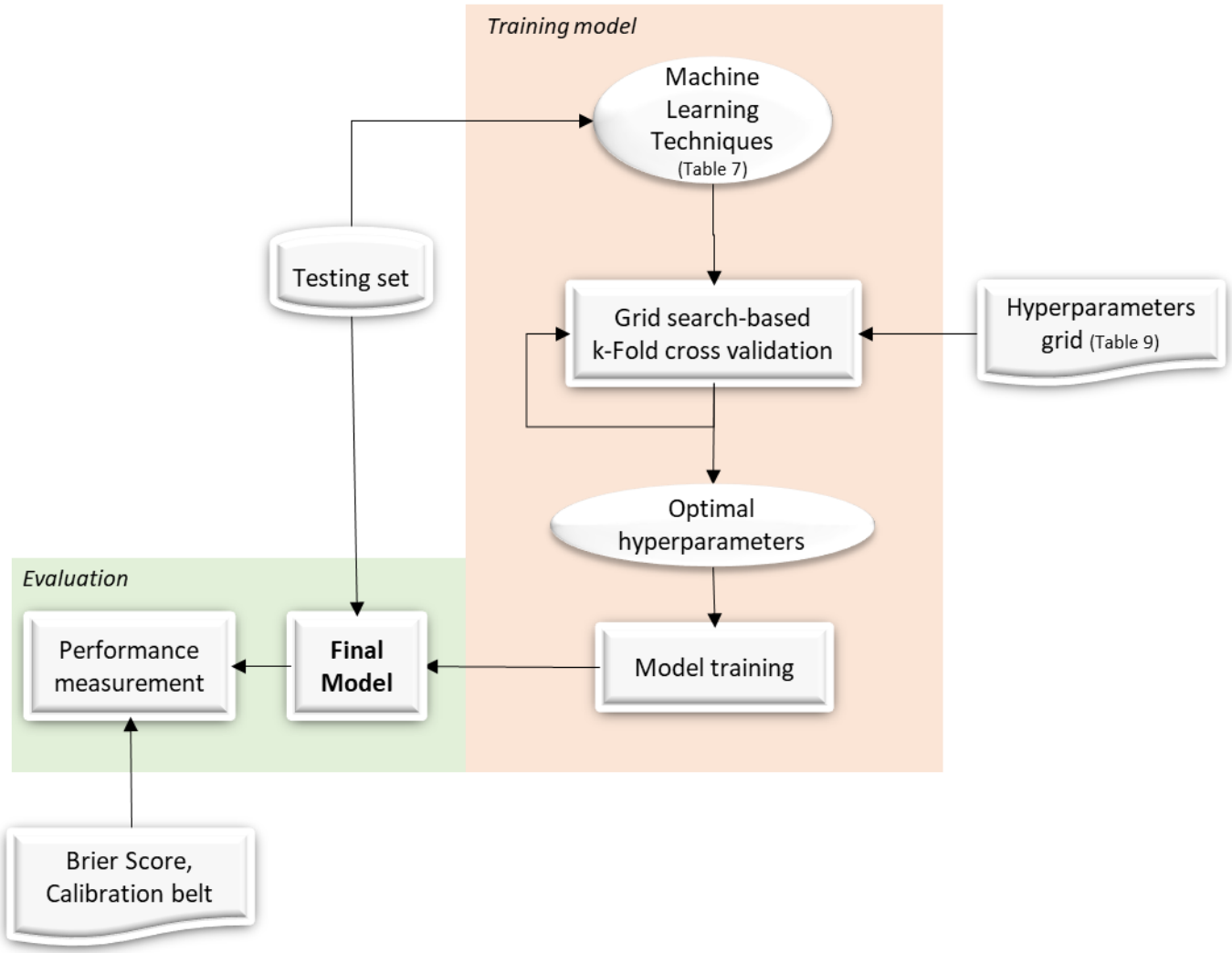
Risk Model for the acquisition of CR-GNB

✓ **Database Preparation**



Risk Model for the acquisition of CR-GNB

✓ **Model building and evaluation**



Risk Model for the acquisition of CR-GNB

✓ Model Building and Evaluation

– General Model

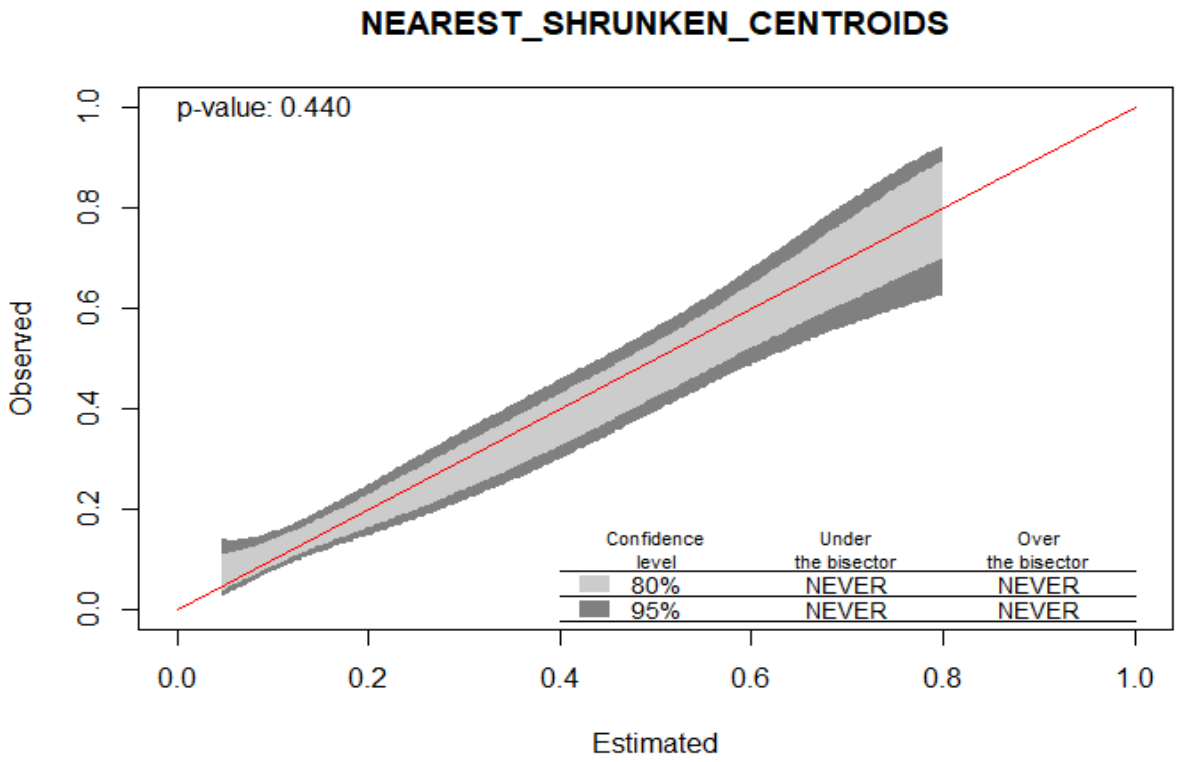
- NSC is the best model to estimate CR-GNB acquisition risk;
- NSC, GBM, CART, LR, LR regularized, and LDA are calibrated models, suitable for prediction;
- NB, Bagging, and RF overestimate the colonization for medium and high-risk patients and underestimates low-risk patients;
- The NB is out almost the whole diagonal line and presented the worst Brier score.

Methods	Brier score	MCC	p-value	Confidence level (80%)	
				Under the bisector	Over the bisector
NSC	**0.152**	**0.327**	√	√	√
GBM	**0.159**	0.312	√	√	√
CART	0.167	0.379	√	√	√
LR	0.163	0.338	√	√	√
LR regularized	**0.155**	0.318	√	√	X
LDA	**0.159**	0.327	√	√	√
SVM RADIAL	0.171	0.109	X	√	X
C45	0.165	0.383	X	X	X
NN	0.160	0.335	X	√	X
ADABOOST	0.172	0.295	X	X	√
C50	0.160	0.399	X	√	X
kNN	0.173	0.296	X	√	X
RF	0.176	0.326	X	X	X
BAGGING	0.183	0.308	X	X	X
SVM LINEAR	0.177	0.345	X	X	X
NB	**0.196**	**0.339**	X	X	X

Risk Model for the acquisition of CR-GNB

✓ **Model Building and Evaluation**

– **General Model**



- No evidence of the lack of calibration emerges from the calibration belt;
- The model calibration on the development is **acceptable** (p-value = 0.440).

Risk Model for the acquisition of CR-GNB

✓ **Model Building and Evaluation**

– **Model by hospital**

Objective: To understand if the built general model can be used for all hospitals;

- There is not a significant difference between general and the five individual models by Brier scores;
  - T-test → P-value = 1

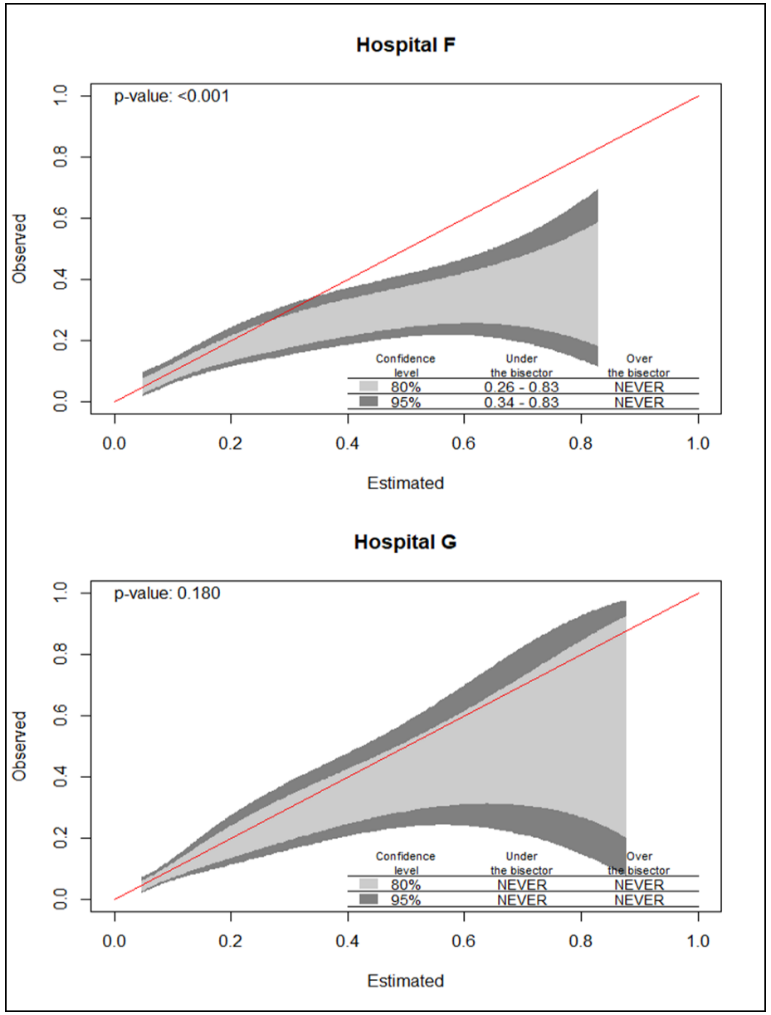
We can use the general model for all hospitals without losing performance;

Risk Model for the acquisition of CR-GNB

✓ External Validation

- Our final risk model for the acquisition of CR-GNB is the NSC;

Hospital	# Patient	#Positive	#Negative	% Positive Tests	Brier Score	MCC
F	267	39	228	14.61%	0.128	0.261
G	357	34	323	9.52%	0.079	0.261
All hospitals - General Model (testing set)	413	105	308	Case-control study (3:1)	0.152	0.327

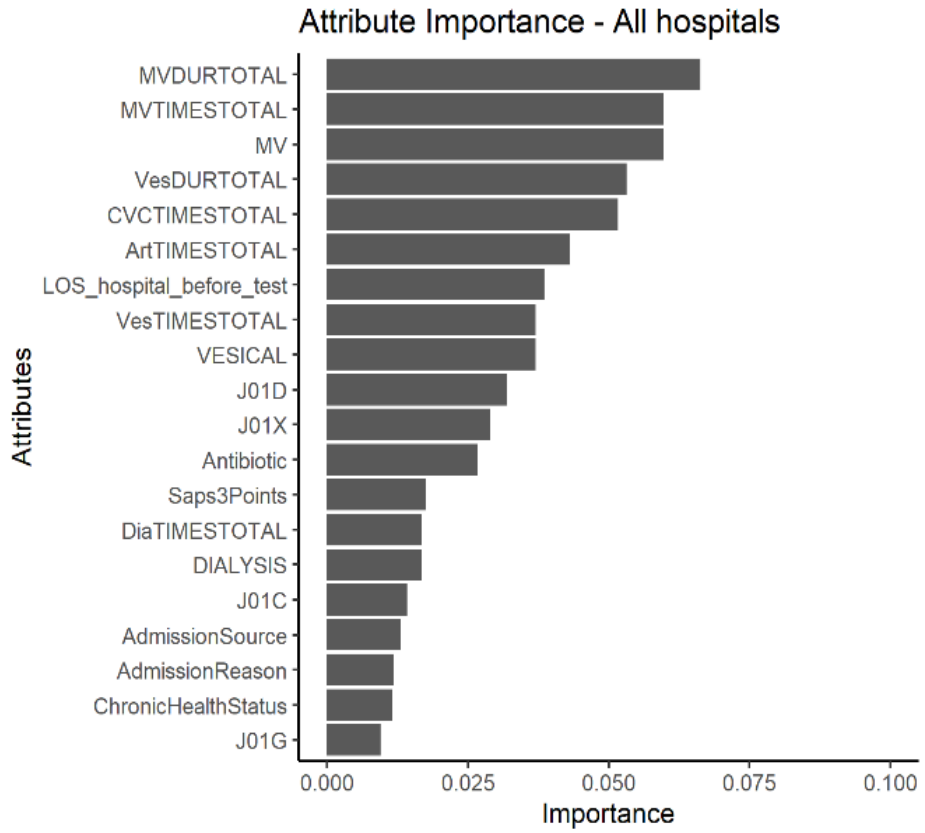


- The model does not classify well the non-acquisition of CR-GNB (MCC = 0.261) but can predict the probability of acquiring (Brier score = 0.128 and 0.079);
- The model is well-calibrated and acceptable to be introduced at Hospital G;
- Hospital F model overestimates the colonization of patients;

Risk Model for the acquisition of CR-GNB

✓ Important of variables

- We identified the attribute importance by Information Gain;



- Duration and use of invasive devices, especially mechanical ventilation;
- Antibiotic groups;
- Admission Source and Admission Reason;
- Criticality indices such as Saps3;
- Length of stay before test.

Risk Model for the acquisition of CR-GNB

✓ Association Rules

- We extracted a list of 157 association rules with predictive value “positive”;
- Example:

#	Rules	Support	Confidence	Lift
1	{MVDURTOTAL=[4,57],VesDURTOTAL=[6,58],J01D=TRUE,Antibiotic=TRUE,VESICAL=YES} => {RESULT=pos}	0.100	0.575	2.257

If a patient is hospitalized with these conditions, this patient has a 57.5% probability of acquisition;

- All the conditions selected include some information about invasive dispositive use;

Discussion

✓ Main Findings – Screening Model

- SMOTEBagging and UnderBagging approaches obtained better results than the data cleaning;
- The more straightforward linear techniques is not significantly different from the more complex classifiers;
- Screening models:
  - Conservative: Random forest → the unnecessary test is avoided **39%** and **8%** of false-negatives.
  - Moderate: Neural Network → the unnecessary test is avoided **64%** and **24%** of false-negatives.

Discussion

✓ Main Findings – Risk Model

- NSC is the best model to estimate acquisition risk;
- Naïve Bayes technique has better discrimination power but the worst Brier score value;
- We can use the general model for all hospitals without losing performance;
- The variables related to the duration of the use of invasive devices, especially mechanical ventilation, are the most important;

Contributions

Literature

- A literature review on prediction in the healthcare context, focusing on multi-resistant bacteria acquisition;
- Evaluation of the different machine learning techniques and balancing strategies;

Methodological

- A framework about "how to conduct a machine learning analysis“;
- Combination of feature selection and cluster techniques;
- An approach to screening modeling considering weekly tests and variables that consider actions that happened between one test and another;

Contributions

Applied

- Rules of strongly associated features that indicate that a patient is at risk of acquired CR-GNB;
- Two screening models: one more conservative and the other moderate;
- A risk model for the acquisition of CR-GNB;

Discussion

✓ Limitations

- These results cannot be directly extrapolated to other healthcare institutions;
- Heterogeneous Gram-negative bacteria were analyzed collectively;
- We do not know precisely how the patient acquired the bacteria;
- Patients with the same conditions may have different types and timing of observations;
- Some records may be lost due to data imputation human errors.

Discussion

✓ Future Researches

- To perform an external validation using the best screening model in new periods and hospitals;
- To develop time-series models considering variable changes over time;
- To compare the relationship of antibiotic use between the periods before and during the pandemic;
- To analyze the influence of acquisition for the patient's outcome within 30 days after a positive test using a survival model.

Discussion

✓ Final Consideration

- Identifying patients who don´t need a weekly culture test decreases hospital costs and laboratory waiting times;
- The models for predicting resistance can offer utility where rapid diagnostics are unavailable or resource impractical;
- Infection control policies can be established to control the spread of these bacteria;
- The framework on how to conduct a machine learning analysis and the code developed can be reusable and easily adaptable;

Publications

*h-index by Scopus = **4***
*h-index by Web of Science = **3***

Articles in Scientific Journals

ANTUNES, B. B. P. ; PERES, I. T. ; BAIAO, F. A. ; RANZANI, O. T. ; BASTOS, L. S. L. ; SILVA, A. A. B. ; SOUZA, G. F. G. ; MARCHESI, J. F. ; **DANTAS, L.F.** ; VARGAS, S. A. ; MACAIRA, P. ; HAMACHER, S. ; BOZZA, F. A. . Progression of confirmed COVID-19 cases after the implementation of control measures. RBTI, v. 1, p. 12-22, 2020. (Cited by Scopus: **2**)

PRADO, M. F. ; ANTUNES, B. B. P. ; BASTOS, L. S. L. ; PERES, I. T. ; SILVA, A. A. B. ; **DANTAS, L.F.** ; BAIAO, F. A. ; MACAIRA, P. ; HAMACHER, S. ; BOZZA, F.A. . Analysis of COVID-19 under-reporting in Brazil. RBTI, v. 00, p. 1-5, 2020. (Cited by Scopus: **4**)

DANTAS, L.F.; DALMAS, B.; ANDRADE, R.M.; HAMACHER, S.; BOZZA, F.A. Predicting acquisition of carbapenem-resistant Gram-negative pathogens in intensive care units. JOURNAL OF HOSPITAL INFECTION, v. 103, p. 121-127, 2019. (Cited by Scopus: **4**)

DANTAS, L. F.; MARCHESI, J. F.; PERES, I. T.; HAMACHER, S.; BOZZA, F. A.; QUINTANO NEIRA, R. A. Public hospitalizations for stroke in Brazil from 2009 to 2016. PLoS One, v. 14, p. e0213837, 2019. (Cited by Scopus: **3**)

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Articles in R1 - Submitted

App-based symptom tracking to optimize SARS-CoV-2 testing strategy using machine learning → PLoS One
Socio-demographic factors associated with COVID-19 in-hospital mortality in Brazil → Public Health

Complete works published in proceedings of conferences

ROCHA, N. G. ; **DANTAS, L. F.** ; HAMACHER, S. ; FIORENCIO, L. ; MARIANI, B. L. ; SOUSA, P. H. . Mineração de Processos aplicada à logística de uma empresa de óleo e gás. In: SBPO, 2019, Limeira. LI Simpósio Brasileiro de Pesquisa Operacional, 2019.

MATTOS, L. M. ; DANTAS, L. F. ; OLIVEIRA, F. L. C. . Análise estatística dos fatores que afetam o no-show de pacientes em agendamentos clínicos. In: SBPO, 2017, Blumenau. XLIX Simpósio Brasileiro de Pesquisa Operacional, 2017.

CUNHA, V. A. M. C. ; DANTAS, L. F. ; BREMENKAMP, L. H. ; PESSOA, L. S. . Dimensionamento de mão de obra e roteamento através de um algoritmo VND: Estudo de caso em uma empresa de medição de consumo de energia. In: SBPO, 2017, Blumenau. XLIX Simpósio Brasileiro de Pesquisa Operacional, 2017.

DANTAS, L. F.; et al. Stairway to value: mining the loan application process. In: International Conference on Business Process Management, 2017, Barcelona. Stairway to value: mining the loan application process, 2017.

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PERES, I. T. ; OLIVEIRA, F. L. C. ; DANTAS, L. F. ; PESSOA, L. S. . Simulação de políticas de agendamento de pacientes em serviços ambulatoriais: uma aplicação em um consultório de ortodontia. In: Simpósio Brasileiro de Pesquisa Operacional, 2016, Vitória. XLVIII Simpósio Brasileiro de Pesquisa Operacional - SBPO 2016, 2016.

BREMENKAMP, L. H. ; MONTEIRO, N. J. ; REPOLHO, H. M. V. ; CUNHA, V. A. M. C. ; DANTAS, L. F. . Aplicação da heurística de Clarke & Wright para um problema de roteirização de veículos homogêneos em uma distribuidora. In: ENEGEP, 2016, João Pessoa. Aplicação da heurística de Clarke & Wright para um problema de roteirização de veículos homogêneos em uma distribuidora, 2016.

CUNHA, V. A. M. C. ; DANTAS, L. F. ; REPOLHO, H. M. V. ; PESSOA, L. S. . Solução heurística para o problema de dimensionamento de mão de obra e roteirização através de um algoritmo Clarke e Wright. In: ANPET, 2016, Rio de Janeiro. ANPET, 2016.

Awards and Titles

2017 Best report Academic Category, BPI Challenge, Business Process Intelligence Workshop.

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THANK YOU!!

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