Healthcare-associated ventriculitis and meningitis in a neuro-ICU: Incidence and risk factors selected by machine learning approach

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ABSTRACT

Purpose: To define the incidence of healthcare-associated ventriculitis and meningitis (HAVM) in the neuro-ICU and to identify HAVM risk factors using tree-based machine learning (ML) algorithms.

Methods: An observational cohort study was conducted in Russia from 2010 to 2017, and included high-risk neuro-ICU patients. We utilized relative risk analysis, regressions, and ML to identify factors associated with HAVM development.

Results: 2286 patients of all ages were included, 216 of them had HAVM. The cumulative incidence of HAVM was 9.45% [95% CI 8.25–10.65]. The incidence of EVD-associated HAVM was 17.2 per 1000 EVD-days or 4.3% [95% CI 3.47–5.13] per 100 patients. Combining all three methods, we selected four important factors contributing to HAVM development: EVD, craniotomy, superficial surgical site infections after neurosurgery, and CSF leakage. The ML models performed better than regressions.

Conclusion: We first reported HAVM incidence in a neuro-ICU in Russia. We showed that tree-based ML is an effective approach to study risk factors because it enables the identification of nonlinear interaction across factors. We suggest that the number of found risk factors and the duration of their presence in patients should be reduced to prevent HAVM.

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1. Introduction

Healthcare-associated ventriculitis and meningitis (HAVM) may take place in association with invasive neurosurgical procedures (post-neurosurgical meningitis), penetrating head trauma (post-traumatic meningitis), or miscellaneous causes on occasion [1]. HAVM significantly impairs patient outcomes, enhancing morbidity and mortality [2]. The development of post-neurosurgical meningitis can

increase mortality rate approximately 3 times (13.7% vs. 4.7%) compared to non-meningitis neurosurgical patients [3]. Moreover, HAVM increases the cost of care. In 2014, Schweizer et al. [4] showed in a large study (>50,000 analyzed operations) a 1.93-fold increase ($23,755 more per case) of attributable health care expenditures to patients with post-neurosurgical meningitis compared to those without infections after neurosurgery. For effective HAVM prevention it is necessary to have reliable data regarding HAVM incidence in different patient cohorts, and learn associated risk factors.

We assigned three primary objectives to this study: (1) to determine the incidence of HAVM in the high-risk population, i.e. patients who stayed in the neuro-ICU for >48 h, (2) to compare HAVM incidence in patients who were exposed to different risk factors during their stay in the ICU and assess relative risk (RR) for each of the factors, and (3) to identify and range HAVM risk factors using regression and machine learning (ML) approaches. We hypothesized that during patients' stay in the ICU a few independent factors would emerge over time, increasing the probability of HAVM development.

The first objective includes the study of HAVM incidence that is usually analyzed depending on risk factors or diagnosis. In the literature, the cumulative incidence of post-neurosurgical meningitis varies

dramatically. While one study demonstrated 0.3% HAVM incidence in 1587 neurosurgical cases [5], another study found 8.6% incidence in 755 pediatric patients after neurosurgery [6]. The incidence of post-traumatic meningitis also varies and depends on trauma features. One study recently reported this rate as 3.1% for all types of brain trauma [7]. Nationwide statistics for HAVM cases in Russia are not publicly available. According to a 2016 state report, 24771 cases of healthcare-associated infections (HAIs) were registered throughout Russia (including 5623 cases of surgical site infections) without distinguishing which were HAVM [8]. The goal of our study is to fill this gap.

Studying of HAVM incidence is particularly relevant for high-risk ICU patients because the admission to the ICU independently increases the risk of HAIs, according to a 2002 report of the U.S. Centers for Disease Control (CDC) [9]. Approximately 25% of all nosocomial infections in the U.S. occurred among adults and children in ICUs [9] despite the fact that ICU beds account for just 8.5% of all hospital beds [10].

The second and third objectives include HAVM risk factors analysis. To date, several different factors have been suggested as possibly increasing the incidence of HAVM. While some of them are well-established, other factors are less certain, and many detected associations are controversial and are not well-supported by data. The craniotomy has been considered to be the main risk factor of HAVM since 1977 [11]. Additionally, invasive devices, e.g. external ventricular drains (EVD), shunts, external lumbar catheters have been shown to increase the rate of HAVM in multiple studies [1,12-14]. The role of other risk factors, including bedside ICPM, reoperation, the duration of neurosurgery, tracheal intubation, central line, and infectious complications of other localizations remains controversial [1,3,5,6].

Typically, researchers use statistical regression models to select disease risk factors [3,6,12,15,16]. However, it has been argued that regression models are not an optimal approach for such a complex problem as HAIs, where nonlinearity can be broadly presented [17]. In addition, linear models have many disadvantages, including sensitivity to data noise and multicollinearity, that can yield misleading conclusions [18]. Thus, the methods used to assess risk factors need to be improved in order to increase reliability and accuracy of the results and prevent HAVM as a final goal.

If we generalize the task of risk factor identification, we come to the well-known data science problem of feature importance ranking [19], a problem that is effectively solved by using ML [19]. We selected the decision tree-based ML algorithms for the study purpose because they are highly effective in feature selection and in dealing with nonlinearity. Specifically, we applied Random Forest (RF) classifier and Extreme Gradient Boosting classifier (XGBoost) to our data set. XGBoost is one of the most successful ML techniques, because it is computationally efficient, scalable, and prevents over-fitting. For instance, feature ranking was successfully performed by using XGBoost in e-commerce, facilitating a reduction in the number of features four times without performance quality loss [20]; the general task was very similar to ours. In medical research, XGBoost is getting more popular for solving binary classifications combined with feature selection [18,22,23]. For example, this approach identified atypical language fMRI patterns in patients with epilepsy and accurately (ROC-AUC = 0.91) distinguished between people with and without disease [21]. The ML algorithms have several advantages over regression models. Particularly important advantages offered by ML include robustness to highly correlated features and noise and the ability to retrieve nonlinear interactions across features and deal with imbalanced data. Moreover, no normalization is needed and fine-tuning parameters can reduce the impact of class imbalance in a training set without rebalancing data.

For the above mentioned reasons, the usage of ML algorithms for the selection of disease-associated risk factors is likely to grow in the future. To the best of our knowledge, no studies using tree-based ML to identify HAVM risk factors have been performed. Herein we proposed XGBoost-based ML algorithm for HAVM risk factors learning in comparison with regression models and RR analysis.

2. Materials and methods

2.1. Study setting and design

This study is a prospective observational single-center cohort study performed in the neuro-ICU at Burdenko Neurosurgery Institute (NSI) in Moscow, Russia. The NSI ICU has 38 single-bed rooms for patients with neurosurgical diseases and cares for approximately 3000 patients per year. In 2010, the program of infection prevention and control was implemented in the ICU. The study analyzed the data collected within this program. We compared two groups of patients, with and without HAVM. Both groups were selected from the high-risk patients' population (see next section).

2.2. Patients and diagnoses

The study lasted for 80 months, from October 1st, 2010 to June 30th, 2017. Only patients who stayed in the ICU for >48 h were eligible. We considered these patients to be a high-risk population and accordingly limited the study to this group only. The exclusion criteria included infections presenting on admission (according to the CDC/NHSN definition [24]) and the duration of ICU stay longer than 1000 days. All qualified patients regardless their age, conditions, disease, etc., were enrolled and participated in the study until discharge or death. Participants were enrolled starting their third to sixth day in the ICU.

HAVM was defined clinically based on the presence of at least three out of eight criteria: (1) CSF glucose level below 2.2 mmol/l or below 50% of plasma glucose in hyperglycemic patients, (2) CSF neutrophils count above 50/μl, (3) CSF protein above 220 mg/dl, (4) CSF lactate above 4.0 mmol/l, (5) positive CSF culture, (6) visualization of bacteria in CSF by Gram staining, (7) SIRS syndrome, (8) negative neurological dynamics. Infection was defined as healthcare-associated if it met the CDC criteria [24]. The case of HAVM was considered to be a factor-related if the patient had the factor (e.g. EVD, ICPM, etc.) for >48 h prior to the development of HAVM, otherwise it was deemed factor-unrelated. At the end of study, we revised HAVM cases for compliance with diagnostic criteria and confirmed them retrospectively.

Due to the open nature of the study, patients were enrolled and then left the study at different points in time. The therapeutic approach and the ICU team remained constant throughout the study. In the follow-up period (after the patient's discharge from the ICU and until the discharge from the hospital) the information regarding the total length of stay and the outcome was collected.

2.3. Data collection and preprocessing

We prospectively collected 54 parameters for each patient, including demographics, exposure to risk factors, infections, etc. (Table 1 Supplementary). The Charlson Comorbidity Index (CCI) value [25] on admission was used to assess the severity of pre-existing conditions. The data were anonymized and stored electronically as a part of NSI's health record system.

For data preprocessing we first inspected data for missing or out-of-range values. We found some occasional missing values and filled them in after retrieving the information from the health record system. If there was no information available in the system, the group mean was substituted for the missing value. Then we expanded the number of variables by generating 175 new clinically relevant aggregation features, and composed a new analytical dataset (available at https://doi.org/10.5281/zenodo.1021503).

2.4. Statistical analysis

Statistical analysis was performed in Python 3.6 using StatsModels [26], SciPy Scientific Tools [27], and scikit-learn [28]. Qualitative variables for dichotomous events are reported as number of events of one

category with percentage and 95% confidence interval (CI) for binomial distribution. Quantitative variables are reported as median with first and third quartiles (Q1;Q3). Cumulative HAVM incidence is presented as the number of HAVM cases per 100 high-risk patients (shown as %). The incidence rate is presented as a number of cases per 1000 patient-days. EVD-associated HAVM incidence was measured using a risk-adjusted, time-dependent denominator: number of cases per 1000 device-days (days at risk). For continuous variables we used a nonparametric statistics (Mann-Whitney test) to test the difference between HAVM and non-HAVM groups. Chi-squared tests were used to compare binary and categorical variables. All statistical tests were two-tailed. Bonferroni-Holm method was used to correct for multiple comparisons where appropriate. The level of significance (p-value) was defined as below 0.01.

In order to estimate the influence of risk factor to the development of HAVM, we stratified patients by the exposure to different risk factors and calculated RR.

Linear models for risk factors selection included principal component analysis (PCA) and multivariate logistic regression. The goal of PCA was to reduce dimensionality into 3-dimensional space and check the possibility of data clusterization. Logistic regression was performed with L1 regularization on the normalized dataset in 10-fold cross-validation using StratifiedKfold algorithm [29]. First, the dataset was checked for multicollinearity and correlated features were removed. We set up the variance inflation factor as a metric to evaluate multicollinearity with threshold = 2.5. The set of not correlated features was entered into the model; odds ratio and 95% CI were calculated for each feature.

2.5. Machine learning for risk factors identification

Machine learning was performed in Python 3.6 using scikit-learn [28]. Categorical variables were converted into dummy/indicator variables. To identify factors associated with HAVM we proposed a two-step algorithm. In the first step, the models were trained to solve binary classification problem for imbalanced classes. In the second step, the model with the best overall performance was used to rank factors by their importance in predicting HAVM.

For the first step we selected four decision tree models: XGBoost with default parameters (XGBoost [30]), XGBoost with scale_pos_weight = 4 (weighted XGBoost), RF with default parameters, and RF with class_weight = 1:4 (weighted RF). Weighted classifiers allowed us to improve performance without using any synthetic data while balancing Type I and Type II errors. Training models were done attempting to maximize "binary:log-loss" objective function (negative log-loss). Since log-loss doesn't discriminate between Type I and Type II errors, we selected four additional metrics to evaluate classification performance: the area under the receiver-operating characteristic curve (ROC-AUC), precision, recall, and F1 score. Stratified Kfold cross-validation algorithm with $k = 10$ was used to prevent models from overfitting [29]. Performance metrics values were calculated as an average of ten cross-validations. The scale_pos_weight value was selected using grid search to achieve at least 25% recall and maximum precision (Fig. 4B Supplementary).

The second and main step of our algorithm is feature selection and ranking. There are several suggested approaches, which can include greedy randomized algorithms, forward selection, and backward elimination [19,31]. XGBoost has a built-in function to estimate feature importance by measuring F-score. We applied this method to each training model because it is validated and computationally effective. However, it does not allow for sufficient reduction in the number of features to reliably compare among them. To increase the accuracy of ranking, we introduced a scoring function which is based on forward feature selection and Top-1 feature rating. Specifically, at each iteration k of the cross-validation, the feature with the highest F-score was picked and one point was assigned to it. Then for each feature we summed up the points to create the ranked list.

2.6. Summary of risk factor identification methods

In total, we applied five techniques to select HAVM risk factors. Four of them (including univariate analysis, multivariate logistic regression, built-in XGBoost F-estimator, and our scoring function) take into account only features that evolved *before* HAVM occurred, i.e. they estimate the probability to develop HAVM in patients with given set of risk factors (or only one factor). Generally speaking, they can be considered predictive algorithms. However, we did not aim to develop the clinical prognostic or early diagnostic model for HAVM, instead using them solely for feature evaluation purposes. The fifth technique, RR analysis, works basically *post-factum* (after HAVM has occurred), and can suffer from confounding variables. Therefore, we hypothesized that the combination of all five methods should yield the optimal and comprehensive result.

Each technique produced a set of important features that then were overlapped. Next, we grouped these features in a clinically appropriate way, counted the number of hits for all features in the group, and then ranked groups by the total number of hits.

2.7. Ethics statement

The NSI Review Board approved the study and granted a consent waiver status. Informed consent from the patient was not required in this case due to non-interventional nature of the study. Also, the study met the criteria 45 CFR 46.117(c) [32] and its Russian analog [33,chapter 4.8.14], indicating that the research presents no more than minimal risk of harm to subjects and does not involve any additional interventions besides those in the regular therapeutic regimen. Characteristics that could potentially identify patients were removed immediately and permanently after the data had been collected to protect the privacy of the patients. The patients and their relatives were provided with the information about the study when asked. Patients did not receive financial compensation.

3. Results

The python code for all steps of data analysis, such as data preprocessing, statistical analysis and ML is available at https://github.com/KseniaErshova/HAVM_paper.git.

3.1. Characteristics of the study population

During 80 months of the study we enrolled 2324 patients. According to the exclusion criteria, 38 patients were removed from the data analysis, leaving 2286 patients in the final dataset (available at https://doi.org/10.5281/zenodo.1021503). Some patients were readmitted to the ICU within one hospitalization, we collected 2519 events of ICU admission from 2286 unique patients with 2087 patients having been admitted once, 168 patients - twice, 30 patients - 3 times, and one patient had 6 events of ICU admission.

A total of 2286 patients included 393 children under 18 years of age (17.2%) and 1139 males (49.8%). Comparing HAVM and non-HAVM groups we found that patients were similar in age, gender, disease type and CCI. A detailed description of two groups is presented in Table 1A. HAVM contributed to more severe overall patients' condition by prolonging the stay in the ICU (42.70 ± 40.98 days [95% CI 36.04; 46.99] vs. 17.82 ± 35.05 days [95% CI 16.31–19.33], p-value < 0.001), and increasing all-cause mortality rate (29.2% [95% CI 23.11–35.23] vs. 13% [95% CI 11.59–14.49], p-value < 0.001), Table 1B.

We diagnosed 216 patients with HAVM, 33 (15.3%) of them being pediatric patients. Two patients had two cases of HAVM during one hospitalization. The median duration of meningitis was 19 days [Q1;Q3: 8;51] with a maximum at 279 days; 38 patients developed HAVM before ICU admission or at the first day in the ICU. For the rest 178 patients the median time between ICU admission and the onset of HAVM was

Table 1

Baseline demographic characteristics (1A) and outcomes (1B) in two groups of patients (with HAVM and without HAVM) included in the study. *p*-Value obtained from Chi-squared or Mann-Whitney test, and corrected to multiple comparisons by using Bonferroni-Holm method. Abbreviations: CI - confidence interval, HAVM - healthcare-associated ventriculitis/meningitis, Q1;Q3 - first and third quartiles.

1A. Demographic characteristics and diagnosis on admission

	Characteristics	All (n = 2286)	HAVM (n = 216)		non-HAVM (n = 2070)		p-Value	Adjusted p-value
		Number of patients (%)	Number of patients (%)	95% CI	Number of patients (%)	95% CI		
	Gender, male	1139 (49.83%)	114 (52.8%)	[46.12–59.44]	1025 (49.5%)	[47.36–51.67]	0.40	1.00
	Children under 18 years of age	393 (17.19%)	33 (15.28%)	[10.48–20.08]	360 (17.4%)	[15.76–19.02]	0.49	1.00
Diagnosis on admission	Brain tumors	1414 (61.85%)	150 (69.4%)	[63.30–75.59]	1264 (61.1%)	[58.96–63.16]	0.02	0.29
	Vascular brain diseases	519 (22.7%)	32 (14.8%)	[10.08–19.55]	487 (23.5%)	[21.70–25.35]	0.00	0.08
	Brain trauma	284 (12.42%)	30 (13.9%)	[9.28–18.50]	254 (12.3%)	[10.86–13.68]	0.56	1.00
	Other diseases	35 (1.53%)	3 (1.4%)	[−0.17–2.95]	32 (1.5%)	[1.01–2.08]	0.91	1.00
	Congenital disorders	28 (1.22%)	1 (0.5%)	[−0.04–0.136]	27 (1.3%)	[0.82–1.79]	0.46	1.00
	Spinal disorders	4 (0.17%)	0 (0.0%)	[0.00–0.00]	4 (0.2%)	[0.00–0.38]	0.83	1.00
		Mean ± Std	Mean ± Std	Median [Q1; Q3]	Mean ± Std	Median [Q1; Q3]	p-Value	Adjusted p-value
	Age	41.9 ± 21.3	41.5 ± 21.0	46 [24.0;56.75]	42.0 ± 21.4	46 [26.0;59.0]	0.28	1.00
	Charlson Comorbidity Index	3.6 ± 2.0	3.7 ± 2.0	3 [2.0;5.0]	3.6 ± 2.0	3 [2.0;5.0]	0.40	1.00

1B. Patients outcomes and types of surgeries which patients underwent throughout the time in the ICU

	Characteristics	All (n = 2286)	HAVM (n = 216)		non-HAVM (n = 2070)		p-Value	Adjusted p-value
		Number of patients (%)	Number of patients (%)	95% CI	Number of patients (%)	95% CI		
Surgery	Craniotomy	1717 (75.11%)	171 (79.2%)	[73.75–84.58]	1546 (74.7%)	[72.81–76.56]	0.1718	1.0000
	Device implantation	704 (30.8%)	144 (66.7%)	[60.38–72.95]	560 (27.1%)	[25.14–28.97]	0.0000	0.0000
	Endonasal transsphenoidal surgery	99 (4.33%)	23 (10.6%)	[6.53–14.76]	76 (3.7%)	[2.86–4.48]	0.0000	0.0001
	Endovascular surgery	227 (9.93%)	22 (10.2%)	[6.15–14.22]	205 (9.9%)	[8.62–11.19]	0.9902	1.0000
	Other surgeries	968 (42.34%)	152 (70.4%)	[64.28–76.46]	816 (39.4%)	[37.32–41.53]	0.0000	0.0000
	No surgery	117 (5.12%)	2 (0.9%)	[−0.35–2.20]	115 (5.6%)	[4.57–6.54]	0.0055	0.0881
	Spinal surgery	51 (2.23%)	5 (2.3%)	[0.31–4.32]	46 (2.2%)	[1.59–2.86]	0.8773	1.0000
Outcome	Death	333 (14.57%)	63 (29.2%)	[23.11–35.23]	270 (13.0%)	[11.59–14.49]	0.0000	0.0000
	Negative dynamics	562 (24.58%)	61 (28.2%)	[22.24–34.24]	501 (24.2%)	[22.36–26.05]	0.2193	1.0000
	No dynamics	243 (10.63%)	13 (6.0%)	[2.85–9.19]	230 (11.1%)	[9.76–12.46]	0.0282	0.3945
	Positive dynamics	1045 (45.71%)	72 (33.3%)	[27.05–39.62]	973 (47.0%)	[44.85–49.15]	0.0002	0.0030
	Recovery	98 (4.29%)	7 (3.2%)	[0.88–5.60]	91 (4.4%)	[3.51–5.28]	0.5345	1.0000
		Mean ± Std	Mean ± Std	Median [Q1; Q3]	Mean ± Std	Median [Q1; Q3]	p-Value	Adjusted p-value
	Total number of days in the ICU	20.06 ± 36.30	42.70 ± 40.98	30 [17.0; 50.5]	17.82 ± 35.05	9 [5.0; 20.0]	0.0000	0.0000
	Total number of days in the hospital	39.66 ± 45.52	74.89 ± 72.94	53 [33.0; 87.5]	36.03 ± 40.41	25 [16.0; 41.0]	0.0000	0.0000
	Number of ICU admission events	1.10 ± 0.36	1.24 ± 0.63	1 [1.0; 1.0]	1.08 ± 0.31	1 [1.0; 1.0]	1.0000	1.0000

9 days [Q1;Q3: 5;15]. Approximately one-third of patients with HAVM developed the disease between the second and seventh day in the ICU (61 patients, 28.2% [95% CI 22.2–34.2]).

3.2. Incidence and relative risk of HAVM for different risk factors

The cumulative incidence of HAVM was 9.45% [95% CI 8.25–10.65], or 4.71 cases per 1000 high-risk patient days in the ICU.

The case of HAVM can be either factor-related or factor-unrelated (see Materials and methods section). We proposed a set of factors, which are likely to increase HAVM incidence in the high-risk patients (candidate factors, listed along x-axis of Fig. 1A). We then calculated incidence and RR of factor-associated HAVM for each individual factor and also for combined factors (Fig. 1A). The highest incidence was found in patients with SSSI (20.2% [95% CI 12.1–28.3], RR = 2.55, *p*-value < 0.001) as compared to those without SSSI. Other significant factors included CSF leak from surgical site (CSFL-SS) (17.5% [95% CI 9.96–25.1], RR = 2.18, *p*-value < 0.001), and implantation of neurosurgical devices (INSD) (17.3% [95% CI 14.5–20.1], RR = 3.81, *p*-value < 0.001). In patients who underwent endoscopic endonasal transsphenoidal surgery (EETS) there was a tendency towards higher incidence rate (17.17% [95% CI 9.74–24.6] vs. 8.82% [95% CI 7.63–10.01], *p*-value = 0.02).

Additionally, we report the distribution of patients with and without HAVM depending on the presence of EVD (Fig. 1B). During the study period EVD was placed in 684 patients, and 99 of them developed EVD-associated HAVM; HAVM incidence in patients with EVD was 14.47% [95% CI 11.8–17.1]. HAVM incidence in patients without EVD was 3.7% [95% CI 2.8–4.6], *p*-value < 0.001, RR = 3.93. The combination of EVD and SSSI is also reported by patients distribution (Fig. 1D) to emphasize its ability to increase HAVM RR as compared to each factor alone (9.4 vs. 3.93 and 2.55 respectively), Fig. 1A&D.

We also stratified patients by risk and assessed the incidence of factor-associated HAVMs using risk-adjusted time-dependent denominators. A total of 2286 patients accounted for 5770 EVD-days and 2494 ICPM-days at risk, and stayed in the ICU for 45,862 days in total. The rate of EVD-associated HAVM was 2.16 cases per 1000 patient-days or 17.16 cases per 1000 EVD-days. For ICPM there were 0.92 cases per 1000 patients-days or 16.84 per 1000 device-days respectively (Fig. 1C). The infection rate in patients without EVD was 1.29 cases per 1000 patient-days, and without ICPM 3.7 cases per 1000 patient-days. The cumulative incidence of EVD-associated HAVM was 4.3% [95% CI 3.47–5.13] per 100 high-risk patients.
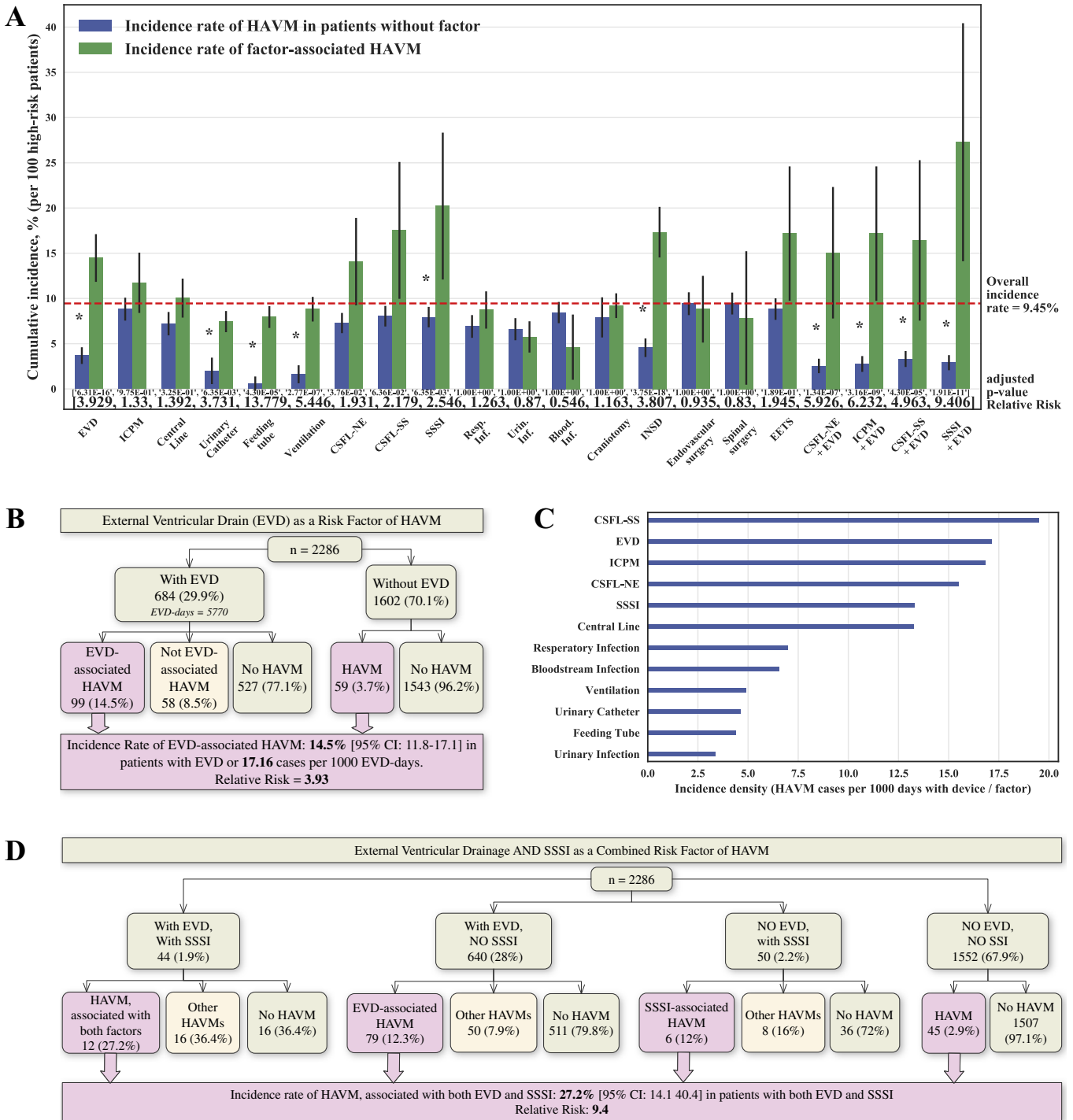
Fig. 1. HAVM incidence in patients exposed to different risk factors in the neuro-ICU. A: cumulative incidence of HAVM, % (cases per 100 high-risk patients) in exposed vs. not exposed patients, errorbars represent 95% confidence interval for binomial distribution; red dashed line represents overall HAVM cumulative incidence; star (*) marks p-value <0.01. B: the distribution of patients with and without HAVM depending on the presence of EVD. C: HAVM incidence density (cases per 1000 days with risk factor). D: the distribution of patients with and without HAVM depending on the presence of either EVD or SSSI or both. Abbreviations: EVD - external ventricular drain; ICPM - ICP monitor; CSFL-NE - CSF leak from nose or ears; CSFL-SS – CSF leak from surgical site; SSSI - superficial surgical site infection after neurosurgery; Resp. Inf.- healthcare-associated respiratory infection; Urin. Inf. - healthcare-associated urinary tract infection; Blood. Inf. - healthcare-associated bloodstream infection; INSD - implantation of neurosurgical devices; EETS - endoscopic endonasal transsphenoidal surgery, HAVM - healthcare-associated ventriculitis and meningitis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Univariate analysis of factors associated with HAVM

We explored factors that can increase the probability of HAVM, by analyzing data only from those patients who had been monitored for at least one day prior to being diagnosed with HAVM. Thus, 178 patients in HAVM group left in analysis. In some cases, HAVM had been

diagnosed 1–2 days later than the actual infection's occurrence, the factors associated with ongoing CNS infection (such as fever, altered conscious level, etc.) were excluded from analysis. The probability density functions for selected continuous variables were different between HAVM and non-HAVM groups, highlighting specific group patterns (Fig. 1A Supplementary).

Here and below we analyzed only factors, reflecting the time before HAVM to evaluate their influence on the probability of HAVM. We performed univariate analysis of 74 variables (Table 2 Supplementary). The distribution of 74 crude *p*-values showed anti-conservative pattern with a high percentage of alternative hypotheses (Fig. 1D Supplementary), which confirmed the validity and reliability of the results [34]. From there, we identified nine factors associated with increased risk of HAVM development (Table 2).

3.4. Linear models for risk factor identification

First, we applied PCA that showed the absence of linear separability between HAVM and non-HAVM groups by using hyperplane (Fig. 1B Supplementary). In addition, cumulative variance explained by PCA showed that at least 60 features (out of 88) should remain to explain 95% of variance (Fig. 1C Supplementary).

The dataset was found to be highly correlated (Fig. 2 Supplementary), that affected the accuracy of feature importance coefficients assessed by logistic regression (Fig. 3C Supplementary). We removed correlated features, leaving 27 features (listed along y-axis on Fig. 2A) in analysis. Two features were shown to increase the likelihood of HAVM: EVD (OR = 1.18 [95% CI 1.06–1.33]) and SSSI (OR = 1.22 [95% CI 1.07–1.38]), and one feature (central line (OR = 0.86 [95% CI 0.79–0.95])) decreased such likelihood (Fig. 2A, Table 3 Supplementary). The performance of logistic regression on the set of not correlated features (*n* = 27) was low (Fig. 2B), with F1 score to be 0.04 (Fig. 2C, red circle). However, F1 score was higher (0.28) on the full data set (Fig. 2C) and the overall performance was better (Fig. 3A&B Supplementary). Therefore, the dataset most likely lost important features during preprocessing, that limits the use of logistic regression in risk factors analysis.

3.5. Tree-based models for risk factor identification

We applied decision tree-based ML algorithms (XGBoost and RF) to identify HAVM risk factors because they are immune to multicollinearity by design and do not require normalization. However, we had to deal with class imbalance problem because the dataset was found to be imbalanced with HAVM patients as a minor class. We tested several techniques: oversampling (SMOTE) [35], undersampling and combinations of evaluation metrics which take into account class imbalance (F1-score). Oversampling minor class using SMOTE led to a decrease in the accuracy of classification, and was not used in the study. The only technique used for dealing with class imbalance was fine-tuned scale_pos_weight parameter of the models.

Weighted XGBoost performed better than other ML models for initial binary classification conducted on the full dataset. Mean of quality metrics over 10 cross-validations demonstrated ROC-AUC = 0.83, precision = 0.39, recall = 0.32, F1 = 0.34, positive predictive value = 0.34, negative predictive value = 0.94 (Fig. 3A&B). It also showed sustainable results on different data subsets with minimal loss of performance quality (Figs. 4, 5, 6 Supplementary). Due to above reasons weighted XGBoost was set up for feature selection. We selected and ranked 42 important factors by F-scoring (Fig. 3D and Fig. 8 Supplementary). Our conservative scoring function identified two important factors over 10 cross-validations including "days with EVD" and "total length of all craniotomies" (Fig. 3E).

When we intersected important factors from five methods (see Materials and methods section), only eight factors out of 42 remained in the list (Fig. 3F). To validate the importance of selected features, they were entered into weighed XGBoost again. The performance metrics decreased insignificantly as compared to the full dataset (F1 = 0.29, ROC-AUC = 0.75). Then permutation test was performed to confirm the result, showing F1 score for eight random features to be 0.13 (Table 4 Supplementary). Thus, the set of eight factors contributes the most to the increased probability of HAVM development, because it explains most of the variance in ML model.

By using ML we also identified factors, which did not have any influence on HAVM development, such as gender, hemodialysis, hypothermia, total parenteral feeding, medical sedation, bloodstream infection, congenital disorders, spinal or other non-brain diseases on admission, and spinal surgery (these factors have F1 = 0 in all ML models).

4. Discussion

We studied two groups of high-risk patients (with and without HAVM) that were similar by age, gender, diagnosis, and comorbidity. However, patients with HAVM had a 2.25 times higher all-cause mortality rate as compared to those without HAVM (attributable mortality was 16.2%). The result is consistent with the literature [3] and highlights the importance of HAVM prevention in a neuro-ICU.

We found the cumulative incidence of HAVM (9.45% or 4.71 cases per 1000 patient-days) that is similar to previously published research. HAVM after craniotomy was registered in 8.6–8.9% of neurosurgical patients [6,12]. The incidence of EVD-associated HAVM was 4.3% [95% CI 3.47–5.13] per 100 high-risk patients or 14.47% [95% CI 11.8–17.1] per 100 patients with EVD. In literature, this value widely varies in different studies reaching 23.2% [15] and even 32.7% [36]. The risk-adjusted incidence rate was found to be 17.16 HAVM cases per 1000 EVD-days. It literature this index also varies: one study found it to be 6.3 per 1000 device-

Table 2
Univariate analysis of different factors for possible association with HAVM in high-risk patients in the ICU. Only factors with adjusted *p*-value <0.01 are shown, for the full result table see Table 2 Supplementary. Chi-squared test was utilized for binary (dichotomous) variables, and Mann-Whitney test was used for ordinal variables. Adjusted *p*-values were obtained by using Bonferroni-Holm method for multiple comparisons.

| Risk Factor	HAVM (n = 216)		non HAVM (n = 2070)		p-Value	Adjusted p-value
	Number of patients (%)	95% CI	Number of patients (%)	95% CI		
External ventricular drain	97 (54.5%)	[47.18–61.81]	527 (25.5%)	[23.58–27.34]	0.0000	0.0000
Central line	154 (86.5%)	[81.50–91.53]	1961 (94.7%)	[93.77–95.70]	0.0000	0.0011
CSF leakage from surgical site (CSFL-SS)	18 (10.1%)	[5.68–14.54]	57 (2.8%)	[2.05–3.46]	0.0000	0.0000
CSF leakage from nose & ears (CSFL-NE)	29 (16.3%)	[10.87–21.72]	135 (6.5%)	[5.46–7.59]	0.0000	0.0002
Superficial surgical site infection after neurosurgery (SSSI)	19 (10.7%)	[6.14–15.21]	52 (2.5%)	[1.84–3.19]	0.0000	0.0000
Implantation of neurosurgical device (INSD)	107 (60.1%)	[52.92–67.31]	560 (27.1%)	[25.14–28.97]	0.0000	0.0000
Other surgeries	115 (64.6%)	[57.58–71.63]	816 (39.4%)	[37.32–41.53]	0.0000	0.0000
Recraniotomy	44 (24.7%)	[18.38–31.06]	270 (13.0%)	[11.59–14.49]	0.0000	0.0017
	Mean ± Std	Median [Q1;Q3]	Mean ± Std	Median [Q1;Q3]	p-Value	Adjusted p-value
Days with lung infiltration on the X-ray	6.94 ± 5.64	7 [2.0; 9.0]	11.60 ± 10.05	9 [5.0; 15.0]	0.0001	0.0073
Days with healthcare-associated respiratory infection	7.23 ± 6.18	7 [2.25; 9.75]	11.88 ± 10.86	9 [5.0; 15.0]	0.0001	0.0075
Count of craniotomies	1.41 ± 0.68	1 [1.0; 2.0]	1.20 ± 0.47	1 [1.0; 1.0]	0.0000	0.0006
Count of implantations of neurosurgical devices	1.92 ± 1.46	1 [1.0; 2.0]	1.33 ± 0.71	1 [1.0; 1.25]	0.0000	0.0000
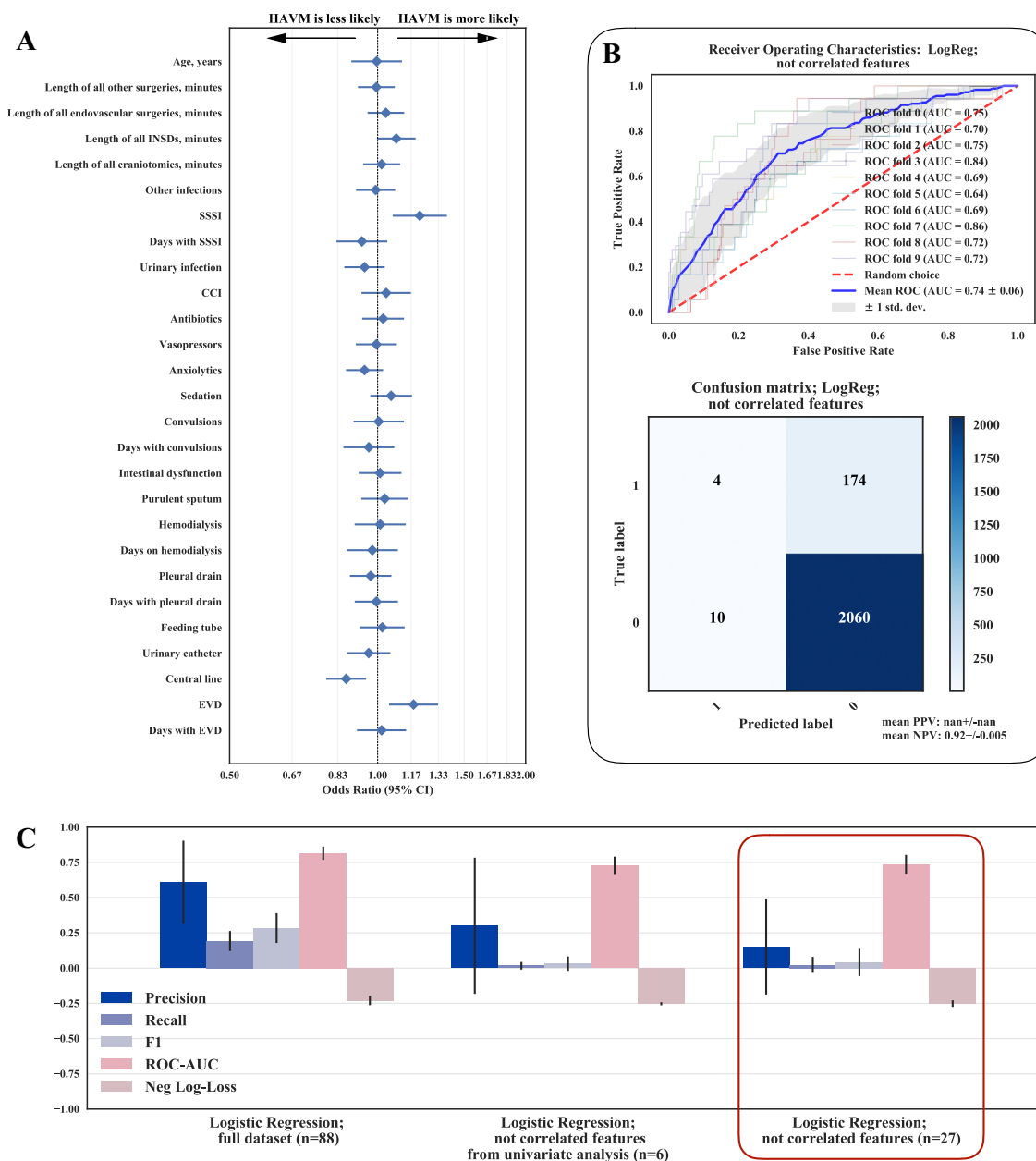
Fig. 2. Multivariate logistic regression on the normalized data set. **A:** odds ratios (OR) of features coefficients, errorbars represent adjusted 95% confidence interval (CI). **B:** ROC-AUC curve and confusion matrix for logistic regression model after 10 cross-validations on the not correlated features. ROC-AUC shows resulting mean curve (blue line) and standard deviation (shadowed grey area), confusion matrix shows mean PPV (positive predictive value) and NPV (negative predictive value); color gradient reflects a proportion of true labels to predicted labels. **C:** performance of logistic regression model on the different datasets - full set of 88 features, not correlated (vif ≤ 2.5) features from the full dataset (n = 27), and not correlated features from statistical inference ($n = 6$) Mean and standard deviation for each metric after 10 cross-validations. Abbreviations: EVD - external ventricular drain; CSFL-NE - CSF leak from nose or ears; CSFL-SS - CSF leak from surgical site; SSSI - superficial surgical site infection after neurosurgery; INSD - implantation of neurosurgical devices; EETS - endoscopic endonasal transsphenoidal surgery, CCI - Charlson comorbidity index. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

days [37], while the other one reported 10.4 per 1000 EVD-days [38]. Relatively high incidence can be explained by specific selection of the high-risk patients' population, and intentionally reduced denominator.

4.1. HAVM risk factors

The overlapping of five lists of important factors resulted in six clinically relevant groups, with five independent groups among them (Fig. 3F). We considered INSD and EVD as dependent variables and analyzed them together.

The most important risk factor is EVD&INSD (nine hits in total). All five methods found EVD to be important, confirming the broadly

accepted thesis that EVD is a risk factor of HAVM [1]. ML-based methods added that the number of days with EVD increases the risk of HAVM. It supports earlier findings that EVD enhances the risk of meningitis proportionally to the number of device-days [1,39].

The second factor associated with HAVM development is craniotomy (five hits). Three methods identified recraniotomy, the number of craniotomies, and the total length of all craniotomies as important. Thus, the more craniotomies a patient has and the longer they are, the more chances for him to develop HAVM. This finding is clearly in line with earlier reports [1,11]. However, the RR analysis failed to identify craniotomy as a risk factor in a neuro-ICU (Fig. 1A).
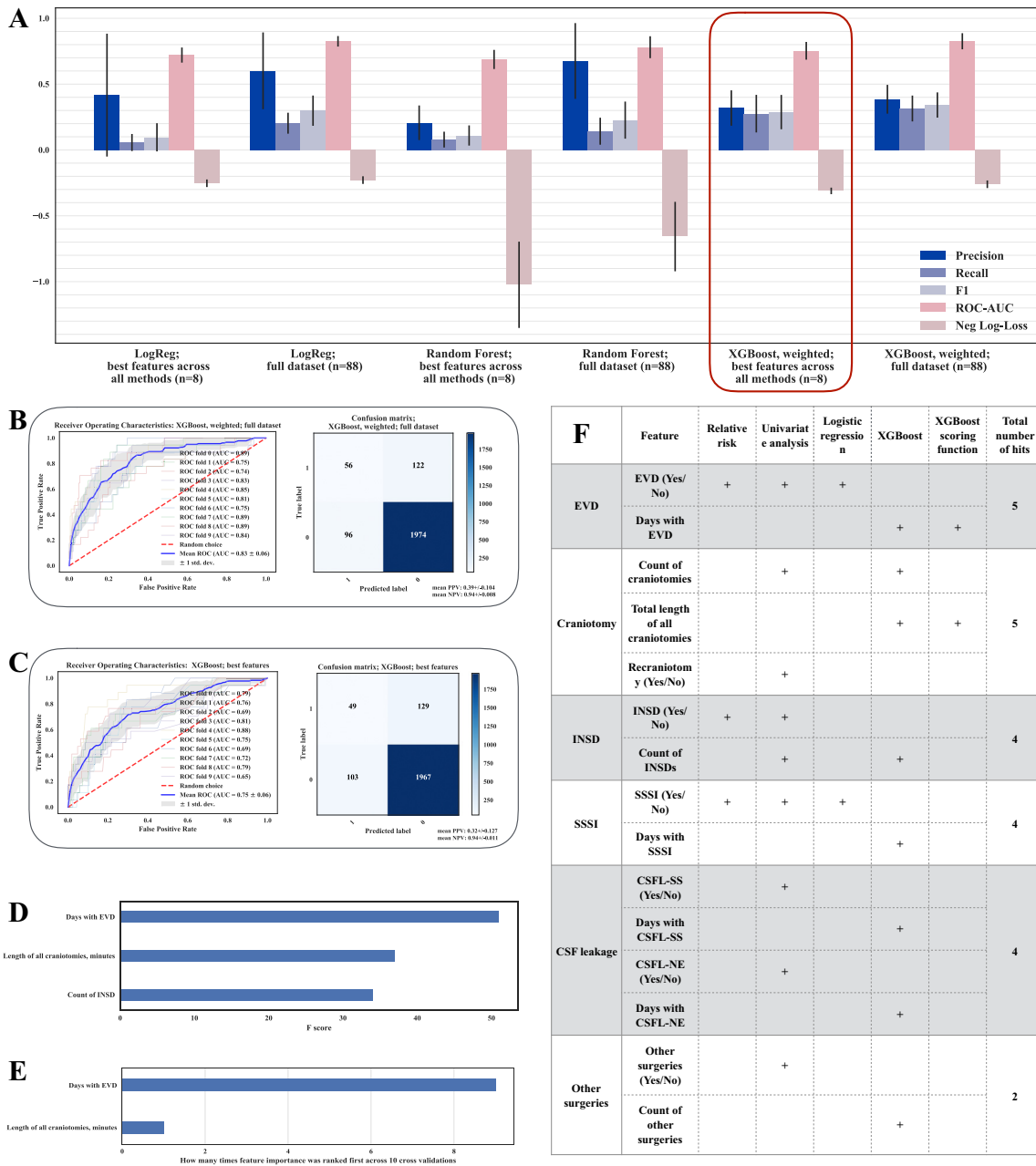
Fig. 3. HAVM risk factors selection. A: comparative performance of logistic regression, XGBoost and Random Forest classifiers on full dataset and on the set of best selected features; mean ± standard deviation after 10 cross-validations are shown for each metrics. B: performance of weighted XGBoost classifier evaluated by ROC-AUC curve and confusion matrix on the full dataset. C: same as B, on the set of best selected features (see in F). D: feature importance resulted from weighted XGBoost classifier and evaluated by F-score, top-3; for the full set see Fig. 8 Supplementary. E: feature importance evaluated by a scoring function (see description in the text) after 10 cross-validations. F: top-6 grouped HAVM risk factors (first column) that include features selected as important (second column) by one of the five evaluation methods (a hit is marked by +). Abbreviations: CSFL-NE - CSF leak from nose and/or ears; CSFL-SS - CSF leak from a surgical site; SSSI - superficial surgical site infection; INSD - implantation of neurosurgical devices; EVD - external ventricular drain.

The next important factor is SSSI (four hits). According to RR analysis, SSSI is an independent factor increasing the probability of HAVM by 2.54 (Fig. 1A). In patients with SSSI the case of HAVM may be called organ/space SSI (according to the CDC definitions of both terms). Thus, we found that the presence of superficial SSI increases the risk of organ/space SSI, which seems to be a reasonable concept, however have not been reported yet for HAVM.

The other important risk factor is CSF leakage from both surgical site and nose/ears. The presence of CSF leak enhances the incidence of HAVM by 1.93–2.18 (Fig. 1A). Also, ML algorithms revealed that the duration of CSF leak is associated with increased probability of HAVM. Previous publications have also mentioned CSF leak as a risk factor of HAVM [1,40].

The last factor on the list (other surgeries) is likely to be a confounding variable. Most of these surgeries were tracheotomy or surgical procedures in combined trauma, that can be considered as a sign of more severe initial conditions in patients with HAVM.

4.2. Practical importance of study findings

We identified four risk factors for HAVM development in high-risk neuro-ICU patients: EVD, craniotomy, SSSI and CSF leak. In accordance with the literature, these factors are common for neuro-ICUs worldwide. Also, they are reproducible and do not depend on clinical/statistical methodology and local clinical practice. Thus, the results from this study may be considered reliable and may be used as an evidence

basis for HAVM prevention strategy development. We suggest that the clinical practice improvement in terms of HAVM prevention can be reached by concentrating efforts on four listed factors. Possible measures can include the decrease of aggressive interventions, the limitation of invasive devices usage with specific attention to the combination of invasive procedures in one patient. In this study, we also found the evidence of the nonlinear nature of HAVM risk factors with most of them being time-dependent. Therefore, one should consider the possibility to remove the invasive device as soon as possible as a result of early risk factors assessment (specifically, four factors mentioned above). We also suggest extensive collaboration with neurosurgeons to prevent CSF leak and the excessive craniotomy duration. In addition, we revealed that endonasal transsphenoidal surgery places the additional risk of HAVM on patients (RR = 1.95) and therefore requires special attention, however, further investigation is needed to figure out the potential reasons for this.

Thus, we encourage clinicians to decrease both the number of risk factors and the duration of their presence to prevent HAVM in the neuro-ICU patients. That said, the development of specific recommendations should be a topic of further research.

4.3. Study limitations

The current study has certain limitations. It is a single-center study in highly specialized ICU facility, thus, one should be careful when generalizing the results to the other hospitals. The surveillance approach was unit-based, but within the ICU we studied only the high-risk patients, not the entire ICU population. Thus, reported HAVM incidence is higher than the one calculated on the entire ICU population. We identified one confounding variable in our analysis, yet it is possible, that there are more than one. The weighted XGBoost model we used for feature selection cannot be used for HAVM prediction in clinical practice. Further research may be done to build effective models for predicting HAVM by using widely known engineering approaches: polynomial features based on EVD days, additional data preprocessing and increasing training samples, and fine-tuning hyper-parameters. However, such predictive models may be difficult to interpret from a clinical point of view due to their complexity.

5. Conclusion

In this study, we assessed the incidence of HAVM and specifically EVD-associated HAVM in a high-risk patient population in a neuro-ICU. It is the first report of this kind from Russia that studies the neuro-ICU facility where evidence-based infection prevention and surveillance program was implemented.

We also showed that in HAVM risk factors analysis, tree-based ML algorithms performed better than regression models and allowed to reveal non-linear time-dependent features. We increased the reliability and accuracy of risk factors selection by combining the results from RR, regressions and ML methods. Thus, we identified four factors associated with HAVM development both by itself and in a time-dependent manner: EVD, craniotomy, superficial SSI, and CSF leakage. These factors are reproducible, do not depend on study methodology and therefore may be used as a ground for planning HAVM prevention strategy. We suggest that the number of found risk factors and the duration of their presence in patients should be reduced to prevent HAVM. However, further research regarding preventive measures is required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.01.022.

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