Machine learning and mHealth techniques to improve prognostication and clinical management of patients with Ebola virus disease

Andres Colubri[1,2,3*], Mary-Anne Hartley[4,5], Mathew Siakor[6], Vanessa Wolfman[6], Tom Sesay[7], August Felix[2], Adam C. Levine[6,8*], Pardis C. Sabeti[1,2,3,9]

[1] Harvard University, Department of Organismic and Evolutionary Biology, Cambridge, MA, USA

[2] Broad Institute of MIT and Harvard, Cambridge, MA, USA

[3] Howard Hughes Medical Institute, Chevy Chase, MD, USA

[4] University of Lausanne, Faculty of Biology and Medicine, Switzerland

[5] GOAL Global, Dublin, Ireland

[6] International Medical Corps. Los Angeles, CA, USA

[7] Sierra Leone Ministry of Health and Sanitation

[8] Brown University, Warren Alpert School of Medicine. Providence, RI, USA

[9] Harvard School of Public Health, Boston, MA, USA

[*] Corresponding authors: acolubri@fas.harvard.edu, alevine@internationalmedicalcorps.org

Abstract

Background: The recent Ebola Virus Disease (EVD) outbreaks have revealed the need for field-deployable tools that can be adapted to the heterogeneous spectrum of the disease across widely varying environments and resources. We previously introduced an mHealth approach for EVD prognostication, where machine learning models were integrated into a mobile application (app) and could be updated with new data. Here, we build upon that approach by generating a new family of models derived from the largest published EVD dataset to date and validated on two independent datasets. These models were incorporated into an app, "Ebola Care Guidelines", that calculates prognosis from the patient data available at triage. The app highlights the signs/symptoms with the largest contribution to the risk of death and provides simplified and targeted access to the recommended supportive care guidelines from WHO.

Methods and Findings: We generated multivariate logistic regression models from 470 patients admitted to five Ebola treatment units (ETUs) in Liberia and Sierra Leone during the 2014-16 outbreak. We handled missing data by multiple imputation and validated the models with two independent datasets from Sierra Leone. Consistent with previous results, viral load and age were the most important predictors of death. We found that observational wellness assessments by experienced health care providers have high predictive power and are able to explain most of the variation due to individual signs/symptoms. We generated a parsimonious model that included (in addition to viral load and age) body temperature, bleeding, jaundice, weakness, and confusion recorded during triage. We also constructed fallback models for when variables in the parsimonious model are unavailable.

Conclusions: This work shows how the integration of prognostic models with mHealth technology can create dynamic and rapidly deployable clinical management support tools that

facilitate tailored access to large bodies of medical information. The Ebola Care Guidelines app was created with a novel clinical decision support framework to develop and update guidelines apps quickly as new data and models became available. The performance of the parsimonious model is very similar to that of the models including the wellness scale from experienced health care workers, suggesting that rigorous machine learning approaches can replicate experienced clinical intuition, and could thus be useful when such expertise is unavailable.

Keywords: Ebola Virus Disease, Prognostic Models, Machine Learning, Data Visualization, Severity Score, mHealth, Supportive Care Guidelines, Clinical Intuition

Introduction

The 2014-2016 outbreak of EVD caused a worldwide health crisis with more than 28,000 cases and 11,000 deaths, the vast majority of which occurred in the West African countries of Liberia, Sierra Leone, and Guinea. The recent outbreak in the Équateur Province of the Democratic Republic of the Congo (1) and the subsequent, still ongoing, outbreak in the North Kivu Province (2) are evidence of the threat posed by EVD, even with the availability of experimental vaccines (3). Of particular concern, is the presence of outbreaks in regions with limited medical coverage such as the active conflict zone affected by the current outbreak.

Despite its notoriety as a deadly disease, the pathology of EVD includes a range of outcomes, spanning from asymptomatic infection to complex organ failure, with case fatality ratios (CFRs) of under 20% achievable in high-income countries where extensive resources can be applied on the few cases that were treated there. Clinical care of highly contagious diseases such as EVD in remote and low-resource settings is far more challenging, hindered by limited availability of trained personnel, restricted time that can be allocated to each patient due to difficult-to-wear personal protective equipment, and lack of supplies. Prioritizing time and material resources for high-risk patients is one approach to decrease overall mortality when subject to such constraints (4). A complementary approach is to use tools providing clinical instructions for management, training, and improved protocol adherence (5, 6).

We previously introduced the use of prognostic models that can be deployed on mobile applications (or apps for short) for the purpose of risk stratification in EVD (7). Prognostic

models can enable the early identification and triage of high-risk patients, which could be useful in low-resource areas to better allocate supportive care. Health care workers could more frequently monitor those patients at increased risk and decide between standard and more aggressive therapy. Our original models were developed on the single publicly available dataset at that time by Schieffelin et al. (8), which includes 106 Ebola-positive patients at Kenema Government Hospital (KGH). These models outperformed simpler risk scores and allowed users to choose from various sets of predictors depending on the available clinical data. While this study showed the potential for such an approach, the models were limited by their geographical relevance (based on a single study site in one country, with a small patient cohort from one period during the outbreak). Furthermore, the prototype app in which the models were packaged was very simple, displaying only the severity score of the patient after the user entered the available clinical features and laboratory tests without further guidance.

We thus sought to create models with greatly expanded geographic relevance packaged in a new app that could provide risk-based guidance to health workers particularly in limited-resource settings. There are comprehensive materials available online, such as WHO and MSF's clinical guidelines for viral hemorrhagic fevers, but these can be difficult to access by health workers in the field due to their book-like presentation, even if they are downloadable as digital files. This makes it hard finding relevant information quickly, tailoring it to the specific characteristics of the patients, or updating it as medical knowledge improves. Recently, a team of critical care and emergency medicine experts employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to develop evidence-based guidelines for the delivery of supportive care to patients admitted to Ebola treatment units (9). These guidelines

are particularly useful as a framework to organize the existing evidence, but still challenging to use for health workers in its current format as a research paper. Our goal is not only to make this information available through an app for health workers, but also tailor and organize care guidelines based on the severity score of the individual patients as predicted by validated prognostic models. In this way, the app could highlight recommendations and interventions that are most relevant given all the available information about the patient during triage.

We created new prognostic models by using the IMC EVD patient cohort, the largest and most diverse available to date (8, 10-14). It is comprised of 470 confirmed cases from five Ebola Treatment Units (ETUs) in Sierra Leone and Liberia, admitted between September 2014 and September 2015. Given the larger sample size and diversity in patient origin, we can expect to generate models that are not overfitted to the characteristics of a specific patient group, and that can be better generalized to new EVD cases. The IMC dataset includes demographic information and clinical signs/symptoms of patients at presentation, RT-PCR Cycle Threshold (CT) measurements (quantifying viral load) done at admission and approaching discharge, daily updates on their signs/symptoms, and observational wellness assessments. The clinical and lab protocols were consistent across the five ETUs, making it possible to aggregate individuals into a single cohort. At the Sierra Leonean ETUs, the health providers also recorded an overall observational wellness assessment of the patients, in the form of a 0 to 5 scale. Such numerical variable encapsulates the provider's clinical gestalt or intuition, resulting from heir accumulated experience in treating hemorrhagic fever patients. This variable also allowed us to compare full or parsimonious models including detailed clinical signs and symptoms with simpler models incorporating the wellness scale alone, and to make conclusions on the predictive power of this

observational scale or, conversely, on the ability of the fully detailed models to recapitulate the clinical gestalt ingrained into the wellness assessment from health providers.

External validation across sites is critical to establish the geographic and demographic range to which the models may be generalized (15). Ideally, the model should be applied to a dataset that was obtained independently from the cases originally used for model training, but even then, porting prognostic models from one center to another is challenging (16). To this end, we report two independent external validations on datasets collected at different health care centers with independent patient catchment areas on patients reporting at different time points of the epidemic. The first, includes the 106 Ebola-positive patients at KGH described by Schieffelin et al. and collected in the first months of the outbreak. The second, described by Hartley et al. (17), comprised 158 Ebola patients who were treated in an ETU run by GOAL global during the final months of the epidemic under conditions that should better represent future outbreak responses.

Methods

IMC Patient Cohort

The cohort used to develop the prognostic models in this study includes patient data collected at five ETUs operated by IMC in Liberia and Sierra Leone between September 15, 2014 and September 15, 2015. The ETUs were located at Lunsar (Port Loko District), Kambia (Kambia District), and Makeni (Bombali District) in Sierra Leone, and at Suakoko (Bong County) and Kakata (Margibi County) in Liberia. The majority of the patients did not come from holding units and presented directly to the IMC ETUs, with an overall Case Fatality Ratio (CFR) across the 5 ETUs of 58%. Collection and archival protocols are detailed in Roshania et al (18). The Sierra Leone Ethics and Scientific Review Committee, the University of Liberia – Pacific Institute for Research & Evaluation Institutional Review Board, the Lifespan (Rhode Island Hospital) Institutional Review Board, and the Harvard Committee on the Use of Human Subjects provided ethical approval for this study and exemption from informed consent. A data sharing agreement was approved by IMC and the Broad Institute, following IMC's Research Review Committee Guidelines (https://internationalmedicalcorps.org/document.doc?id=800).

Data Collection

Trained nurses, physician assistants, physicians, and psychosocial support staff recorded patient demographic, clinical, and support data at least daily from admission to discharge on standardized paper forms – as part of routine clinical care and for epidemiologic purposes. The three ETUs in Sierra Leone also collected the wellness scale (WS) of the patients. WS is an observational assessment of patient wellness assigned by the physician or physician assistants,

recorded at every daily round, and ranging from 0 (cured) to 5 (very sick patient), as described in Table 1. Local data officers entered this data into separate electronic databases at each ETU, which were combined together into a unified database. The RT-PCR data were obtained from four laboratories. The United States Naval Medical Research Center Mobile Laboratory in Bong County, Liberia, served the Bong and Margibi ETUs; the Public Health England (PHE) labs in Port Loko and Makeni in Sierra Leone processed samples from Lunsar and Makeni; the Nigerian Lab served the Kambia ETU.

Wellness Scale	*Interpretation*
0	Cured
1	Well: no symptoms: drinks and eats okay
2	Few symptoms: drinks and eats okay
3	Moderate symptoms: can walk, sit, and feed self
4	Sick: needs help to be fed, drink, and take medications
5	Very sick: needs IV fluids and medications, lots of help

Table 1. Wellness scale. Interpretation of the 0-to-5 observational scale of patient wellness at the Sierra Leonean ETUs.

Exploratory and Univariate Analysis

The primary variable of interest for patients admitted to the ETUs was final outcome (death or survival). The outcome of 5 patients was missing due to being transferred to another facility. The Cycle Threshold (CT) value is an inversely proportional proxy of viral load, with a cut-off of 40 cycles considered as negative. These values were calculated from PCRs performed on admission, or from the second PCR when the first was missing (performed no later than two days after admission and affecting 155 cases). We carried out an initial univariate analysis of all factors

against disposition, using the χ^2 test with Yates correction for the binary variables, and the point biserial correlation test for numerical variables.

Logistic Regression with Multiple Imputation

We constructed several logistic regression models to predict the binary outcome death/survival from the demographic, clinical, and laboratory data available at triage. The main challenges in the modeling task were the high occurrence of missing values, and the lack of a pre-specified prognostic model. We handled missing data by generating multiple imputations with the aregImpute function from the Hmisc package for the R statistics software. This function generates a Bayesian predictive distribution from the known data, and outputs a number N of imputed datasets. Each missing value in the ith imputation is predicted from an additive model fitted on a bootstrap sample with replacement from the original data. We set N=100, well above standard imputation guidelines (19). In order to construct the prognostic models, we first reviewed published research on the factors associated with death in EVD. We then complemented this prior knowledge with a variable selection procedure based on penalized logistic regression implemented with the R package Glmnet. We used an equal mixture of L1 and L2 penalties, also called Elastic Net regularization. The selection procedure consisted of fitting N times (one for each imputation) a fully saturated model including all variables, and then calculating the number of times the regression coefficient of each sign/symptom was greater than zero, thus indicating a positive association with death. We kept the sign/symptoms that were greater than zero in at least half of the penalized models. Once we identified a subset of variables in this manner, we constructed a family of non-penalized logistic regression models with the function lrm from the R package rms. This family includes a parsimonious model with all the

variables obtained from the selection process, but also models that can be applied on smaller subsets of demographic information, clinical features and laboratory results, allowing us to use a less detailed model if not all variables are available at triage. This approach has been shown to outperform predictive value imputation, which consists of having only one full model and imputing missing values at prediction time using the data distribution from the training set (20). Each final model in the family was obtained by fitting N copies of the model on each imputed dataset, and then averaging those copies into a single model using the fit.mult.impute function in Hmisc. We conducted internal validation of the models using bootstrap resampling in order to obtain unbiased estimates of model performance without decreasing sample size.

External Validation

We did two external validations on independently collected datasets from Sierra Leone. The KGH dataset described by Schieffelin et al. (8) is the only such database to be made publicly available at the time of this study (https://dataverse.harvard.edu/dataverse/ebola). It includes 106 EVD-positive cases treated at KGH between May 25 and June 18, 2014. CFR among these patients was 73%. Sign and symptom data were obtained at time of presentation on 44 patients who were admitted and had a clinical chart. Viral load was determined in 58 cases. Both sign and symptom data and viral load were available for 32 cases. We generated 50 multiple imputations with MICE to apply the IMC models on the KGH cases with incomplete data. The GOAL dataset described by Hartley et al. (17, 21) includes 158 EVD-positive cases treated at the GOAL-Mathaska ETU in Port Loko between December 2014 and June 2015, where the CFR was 60%. Ebola-specific RT-PCR results and detailed sign and symptom data was available for all 158 patients. The Ebola-specific RT-PCRs recorded in the GOAL dataset were performed by

the same PHE laboratory system as for the majority of the Sierra Leonean IMC data. Average CT values reported in this dataset between survival and fatal outcomes were not statistically different from that recorded by the IMC.

The KGH dataset includes RT-PCR data as viral load (VL) quantities expressed in copies/ml, but the corresponding CT values are no longer available. Since the IMC models use CT as a predictor, we transformed log(VL) to CT by solving for the standard qPCR curve transformation $\log(VL) = m \times CT + c0$, such that the minimum VL in the KGH dataset corresponds to the maximum CT in the IMC dataset, and vice versa. The assays used for diagnosing patients at KGH and IMC have very similar limits of detection (22-24), which justifies the methodology of our VL-to-CT transformation. We also note that a ≈10-fold increase in Ebola VL corresponds to a 3-point decrease in CT (25). Based on this relationship, $-3/m$ in our formula should be close to 1, which is indeed the case ($-3/m=0.976$ using the m and c0 constants derived from the KGH and IMC data).

A Framework for Developing Clinical Guideline Apps

We created a general framework to integrate available patient care and management guidelines with clinical prediction models into mobile apps for health workers. This framework takes as input a list of guidelines provided as PDF documents, model specifications including input variables, coefficients, and ranges for each term in the model (it only supports logistic regression models at this time), a list of recommendations where each entry is linked to a subset of interventions described in the guideline documents and a subset of input variables in the models, and various app resources (icon images, message strings). These materials are compiled into a

stand-alone app for the Android mobile Operating System. All the documents and text resources can be provided in multiple languages so that the app is properly internationalized depending on the intended country or region of deployment. The resulting app offers a simple user interface to access the clinical interventions described in the guidelines, organized into separate recommendations of care. Patient data can be entered into the app either through its own data entry interface, or via a separate CommCare (https://www.commcarehq.org) app for front-line data collection. The app also offers an interactive visualization of the severity score calculated with a model applicable to the provided patient data. This visualization uses the patient-specific charts described by Van Belle and Van Calster (26), which were designed to visualize the contribution of each term in a logistic regression model to the total prediction score.

Results

Prognostic Potential and Prevalence of Signs and Symptoms Recorded at Triage

Triage symptoms reported by over 50% of fatal Ebola patients were anorexia/loss of appetite, fever, weakness, musculoskeletal pain, headache and diarrhea (Table 2A). Few variables were significantly associated with patient outcome, suggesting that most clinical signs and symptoms have little predictive ability on their own, at least when considered at triage alone. Only CT, age (Table 2B), and jaundice (Table 2A) were associated with death at a level of $P<0.05$, while red eyes, confusion, breathlessness, headache, and bleeding were weakly associated at $P<0.15$. However, statistical association of the variables when taken alone might be due to confounding effects in the data. Also, the prevalence of several triage symptoms was notably different between fatal and non-fatal outcomes, as can be seen by comparing their ranking (Suppl. Figure 1A) or their differential prevalence (Suppl. Figure 1B).

Table 2A

Variable	*Total %*	*Non-fatal %*	*Fatal %*	*Missing %*	*OR 95% CI*	*P-value*
Jaundice	24/464 (5)	4/197 (2)	20/267 (7)	1/470 (0)	3.91 (1.31, 11.62)	0.016
Red eyes	128/464 (27)	64/197 (32)	64/267 (23)	1/470 (0)	0.66(0.43, 0.99)	0.054
Coma	5/178 (2)	0/83 (0)	5/95 (5)	292/470 (62)	NA	0.096
Confusion	16/178 (8)	4/83 (4)	12/95 (12)	292/470 (62)	2.86 (0.88, 9.23)	0.120
Breathlessness	109/464 (23)	39/197 (19)	70/267 (26)	1/470 (0)	1.44 (0.92, 2.24)	0.133
Headache	268/464 (57)	122/197 (61)	146/267 (54)	1/470 (0)	0.74 (0.51, 1.08)	0.142
Bleeding	26/464 (5)	7/197 (3)	19/267 (7)	1/470 (0)	2.08 (0.86, 5.05)	0.148
Asthenia/Weakness	334/464 (71)	135/197 (68)	199/267 (74)	1/470 (0)	1.34 (0.89, 2.02)	0.187
Diarrhea	234/430 (54)	96/187 (51)	138/243 (56)	35/470 (7)	1.25 (0.85, 1.83)	0.304
Malaria	49/225 (21)	17/94 (18)	32/131 (24)	241/470 (51)	1.46 (0.76, 2.83)	0.331
Swallowing Problems	112/464 (24)	43/197 (21)	69/267 (25)	1/470 (0)	1.25 (0.81, 1.93)	0.374
Vomiting	197/464 (42)	87/197 (44)	110/267 (41)	1/470 (0)	0.89 (0.61, 1.29)	0.587
Nausea	94/286 (32)	35/114 (30)	59/172 (34)	179/470 (38)	1.18 (0.71, 1.96)	0.613

Abdominal Pain	203/464 (43)	89/197 (45)	114/267 (42)	1/470 (0)	0.90 (0.62, 1.31)	0.662
Bone/Muscle/Joint Pain	272/465 (58)	118/197 (59)	154/268 (57)	0/470 (0)	0.90 (0.62, 1.31)	0.666
Throat Pain	55/178 (30)	24/83 (28)	31/95 (32)	292/470 (62)	1.19 (0.63, 2.26)	0.709
Cough	61/178 (34)	30/83 (36)	31/95 (32)	292/470 (62)	0.86 (0.46, 1.59)	0.738
Hiccups	55/464 (11)	22/197 (11)	33/267 (12)	1/470 (0)	1.12 (0.63, 1.99)	0.805
Rash	8/178 (4)	3/83 (3)	5/95 (5)	292/470 (62)	1.48 (0.34, 6.40)	0.867
Chest Pain	88/178 (49)	41/83 (49)	47/95 (49)	292/470 (62)	1.00 (0.56, 1.81)	0.889
Photophobia	24/178 (13)	11/83 (13)	13/95 (13)	292/470 (62)	1.04 (0.44, 2.46)	0.892
Anorexia/ Loss of Appetite	316/465 (67)	135/197 (68)	181/268 (67)	0/470 (0)	0.95 (0.64, 1.42)	0.900
Fever	349/464 (75)	148/197 (75)	201/267 (75)	1/470 (0)	1.01 (0.66, 1.54)	0.944

Table 2B

Variable	*Mean non-fatal cases (95% CI)*	*Mean fatal cases (95% CI)*	*Missing fraction (%)*	*Pearson's R*	*Odds-Ratio (95% CI)*	*P-value*
Cycle Threshold	26.72 (15.92, 37.52)	22.23 (11.18, 33.28)	29	-0.371	0.331 (0.23, 0.47)	<0.0001
Patient Age	28.49 (0.00, 58.72)	32.03 (0.00, 72.10)	0	0.095	1.326 (1.01, 1.74)	0.043
Body Temperature	37.41 (35.50, 39.32)	37.67 (35.34, 40.01)	56	0.116	1.391 (0.94, 2.06)	0.099
Days of Fever	3.44 (0.00, 7.74)	3.56 (0.00, 7.90)	74	0.025	1.048 (0.74, 1.48)	0.79

Table 2. Univariate analysis. Correlation between either binary (A) or continuous (B) clinical variables and the outcome of death. Marginal odds-ratios were obtained from the univariate logistic regression model for death using each variable alone as a predictor. For continuous variables, the Pearson's R correlation coefficient is used and the odd-ratios correspond to inter-quartile range changes in the predictor.

Performance of Multivariate Logistic Regression Models

Our family of multivariate logistic regression models includes a parsimonious model with the most informative variables in our data. Several studies have previously identified single signs and symptoms statistically predictive for EVD mortality (17), such as high viral load (10, 11, 27, 28), hemorrhagic signs (10, 29, 30), confusion (11, 29, 31), extreme fatigue (31), and asthenia (27, 31). Taking this existing medical knowledge on EVD into consideration, and applying the

variable selection procedure described in the methods, we reached a parsimonious set of variables including patient age as the only demographic parameter, the first available cycle time (CT) from PCR, malaria test result, and the clinical signs/symptoms of body temperature, bleeding, jaundice, breathlessness, asthenia/weakness, and confusion recorded during triage. We use restricted cubic splines to model the non-linear relationships between CFR and age (Suppl. Figure S2A) and CFR and body temperature (Suppl. Figure S2B). Inspection of the CFR vs CT plot (Suppl. Figure S3) indicated that cubic splines were not required to model CT. In addition to the parsimonious model, we also constructed a parsimonious-minus-malaria model, which could be used when the malaria test result is not available, a clinical-only model that includes neither CT nor malaria test result, so that it could be useful at ETUs without access to laboratory facilities, and a minimal model only incorporating CT and age, which are the strongest predictors of outcome on their own, as observed in our data and reported by other researchers (14). Table 3 contains the validation indices of these four models. The bias-corrected C statistic (also known as the area under the receiver characteristic curve, or AUC) is highest for the parsimonious model at 0.79, 0.78 for the parsimonious minus-malaria, 0.68 for the clinical-only model, and 0.75 for the minimal model. In general, all the indices are fairly similar across the three models excluding the clinical-only model that shows consistently inferior performance.

	Parsimonious	*Parsimonious w/out malaria*	*Clinical-only*	*Minimal*
AUC	0.791	0.780	0.678	0.751
R^2	0.264	0.270	0.109	0.247
Brier	0.188	0.192	0.224	0.206
Discrimination	0.212	0.219	0.080	0.200
Unreliability	0.006	0.004	0.004	0.001
Quality	0.206	0.216	0.076	0.199

Table 3. Validation indices for the prognostic models. These indices include the AUC (area under the ROC curve or C-statistic), the R^2 goodness-of-fit index, and the Brier, discrimination, unreliability, and quality scores. Obtained with the validate.lrm function in the rms package.

Examination of the estimated calibration curves comparing the predicted and actual probabilities of death (Figure 1) indicate that all models with the exception of the minimal exhibit good calibration. These results from the internal bootstrap validation, taken together, suggest that the parsimonious model is indeed the best performing one.

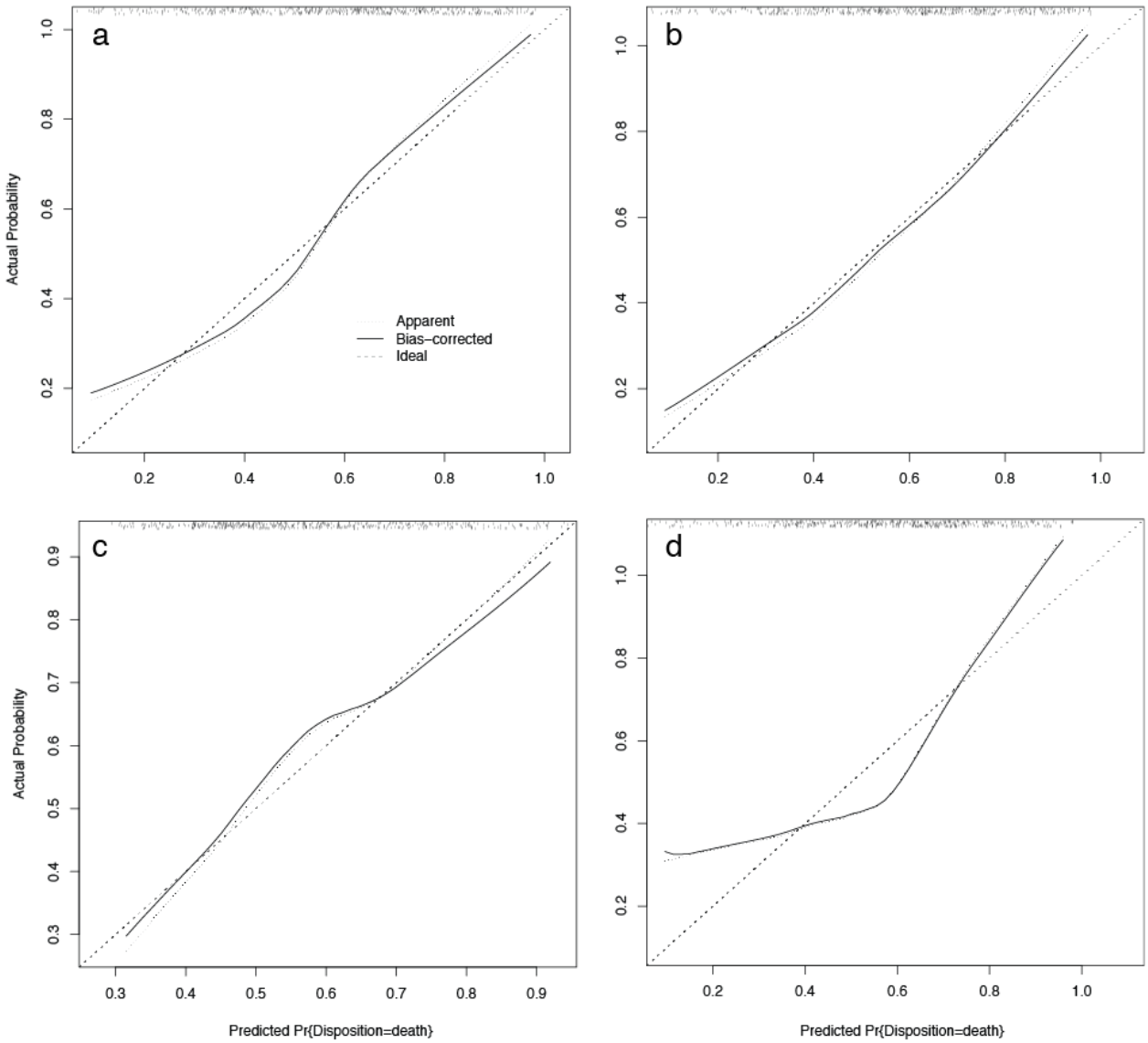

Figure 1. Bootstrap overfitting-corrected calibration curve. Estimated for the four prognostic models: parsimonious (a), parsimonious without malaria (b), clinical-only (c), and minimal (d). Each plot contains the rug chart at the top showing the distribution of predicted risks. Generated with the calibrate function in the rms package.

The ranking of all of the variables by their importance in the parsimonious model, as measured by the Wald χ^2 statistic, also indicates that the most important variables are CT and patient age, with jaundice and bleeding coming in at a distant third and fourth place respectively (Figure 2A). The odds ratios of these variables (Figure 2B) indicate that presentation of either jaundice or bleeding are associated with more than a doubling of the risk of death, although their prevalence is low at 5% (Table 2). Other signs/symptoms have a very low predictive importance and small effect in the death risk.

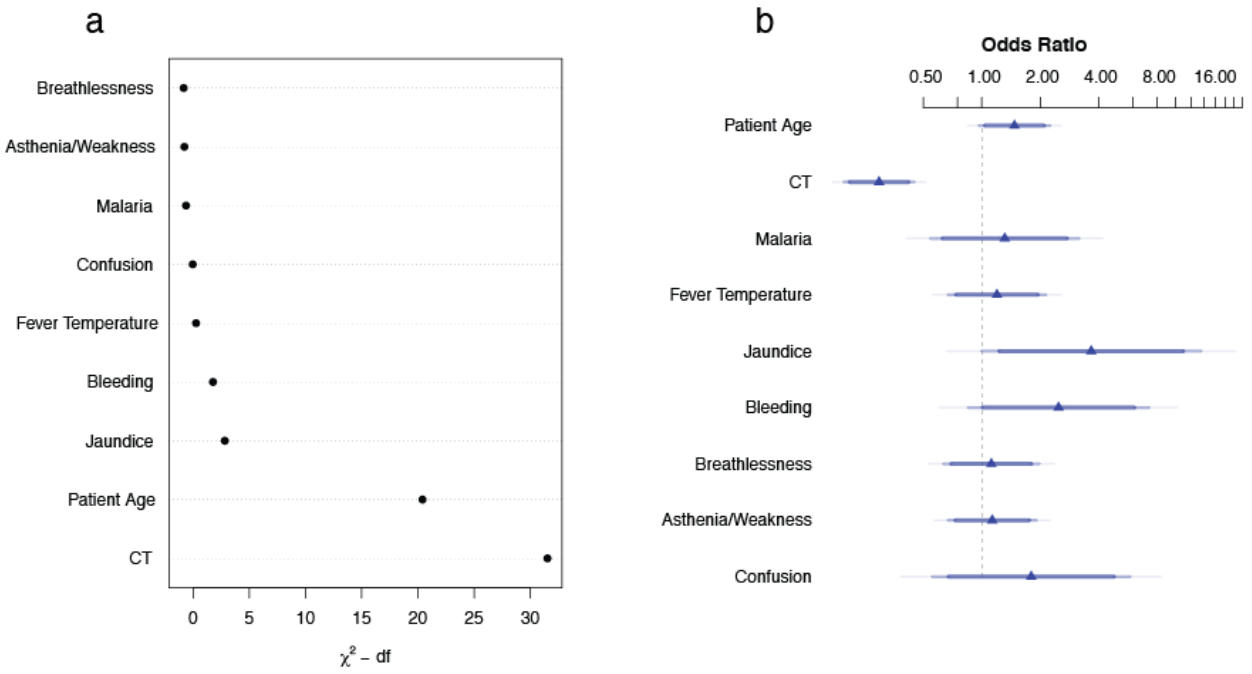

Figure 2. Evaluation of predictor variables in the parsimonious model. Ranking of the variables according to their predictive importance in the model, as measured by the χ^2-d.f. (degrees of freedom) statistic (a). Odds ratios for all the variables, using interquartile-range odds ratios for continuous features, and simple odds ratios for categorical features (b). Generated with the anova.rms (a) and summary (b) functions in the rms and base packages in R.

External validation

External validation on the 158 EVD-positive patients in the GOAL dataset shows that the four models described earlier actually improve their performance with respect to the internal validation, with AUC of 0.848, 0.838, 0.718 and 0.845 for the parsimonious, parsimonious without malaria, clinical-only, and minimal (Table 4). In terms of the accuracy, sensitivity, and specificity, (calculated using a 0.5 threshold in the score of the logistic model to define a death vs survival prediction), all the models, with the exception of the clinical-only, perform similarly well with accuracies over 70%. Lack of viral load data causes accuracy in the clinical-only model to drop below 60%.

	Parsimonious	*Parsimonious w/out malaria*	*Clinical-only*	*Minimal*
AUC	0.848	0.838	0.718	0.845
Brier	0.166	0.165	0.272	0.172
Accuracy	0.731	0.722	0.567	0.750
Sensitivity	0.896	0.860	0.779	0.907
Specificity	0.509	0.517	0.510	0.517

Table 4. External validation on the GOAL dataset. The AUC, Brier, accuracy, sensitivity, and specificity indices were calculated on all the records from the GOAL dataset that had enough data to evaluate the models. Less than 1% of the data was excluded due to incompleteness.

External validation on the KGH dataset required to fit an alternative parsimonious model, since not all the variables in the original parsimonious model trained on the IMC data were available in this cohort of patients. The same selection process led to a KGH-compatible parsimonious model including CT, patient age, jaundice, bleeding, sore throat, asthenia/weakness, and confusion. We also constructed a corresponding KGH-compatible clinical-only model. We fitted these two additional models on the IMC data, and conducted external validation on the KGH data. The results are shown in Table 5, where the AUC of the KGH parsimonious model is very high at 0.95. Accuracy, sensitivity and specificity are also high, however, only 32 KGH patients with all the required clinical data could be included in the validation step. In the case of the minimal model, it was possible to apply it to the KGH dataset without any modifications, and 63 patients from this dataset had all the values (age and CT) required by the model. The performance is also high with an AUC of 0.814.

	KGH parsimonious	*KGH clinical-only*	*minimal*
AUC	0.948	0.845	0.814
Brier	0.219	0.223	0.199
Accuracy	0.875	0.860	0.730
Sensitivity	0.889	0.972	0.689
Specificity	0.800	0.286	0.833

Table 5. External validation on the KGH dataset. The AUC, Brier, accuracy, sensitivity, and specificity indices were calculated on all the records from the KGH dataset that had enough data to evaluate the models. Only 32 records could be used in the KGH parsimonious and clinical-only models, but 62 had enough data to evaluate the minimal model.

Wellness Scale Models

We constructed four additional models incorporating the wellness scale (WS) variable in place of the detailed clinical signs and symptoms used in the previous models: wellness+lab (including CT, patient age, malaria, fever temperature, and WS), wellness+lab without malaria, wellness clinical-only (including patient age, fever temperature, and WS), and wellness minimal (including CT, patient age, and WS). The performance indices of these models, obtained from internal validation on the entire IMC data, are shown in Table 6.

	Wellness+lab	*Wellness+lab w/out malaria*	*Wellness clinical-only*	*Wellness minimal*
AUC	0.774	0.806	0.715	0.775
R^2	0.291	0.295	0.201	0.293
Brier	0.194	0.181	0.212	0.194
Discrimination	0.241	0.243	0.160	0.243
Unreliability	0.003	0.001	0.000	0.001
Quality	0.238	0.242	0.160	0.242

Table 6. Validation of the wellness scale models. These models were evaluated using the same indices of performance as the previous models: AUC, R^2, Brier, discrimination, unreliability, and quality scores. Obtained with the validate.lrm function in the rms package.

The AUC of these models is comparable with that of the original four models that include detailed clinical signs and symptoms (Table 3). In fact, the R^2 statistic, which indicates a model's goodness-of-fit to the data, is higher at 0.291 (vs. 0.264 in the parsimonious model) and the quality index, defined as discrimination minus unreliability is also higher at 0.238 (vs. 0.206 in the parsimonious model). Even the wellness clinical-only, without viral load or malaria test result data, performs better than the clinical-only model that includes jaundice, bleeding, breathlessness, asthenia/weakness, diarrhea, and confusion, with a bias-corrected AUC of 0.715

vs 0.678 in the latter. The calibration curves for these four wellness models are also consistently close to the 45° diagonal, indicating a good correspondence between predicted and actual probabilities (Figure 3).

The wellness assessments were available only for the patients treated at the three ETUs in Sierra Leone, and so the WS value was imputed for the rest of the patients. To evaluate the effect of imputation in the models, we fitted the four wellness models only on those patients with known WS (a total of 223). The performance of the refitted models (Suppl. Table S1) is consistent with that of the original models, although slightly higher, which is expected due to the variance inflation caused by the imputation.

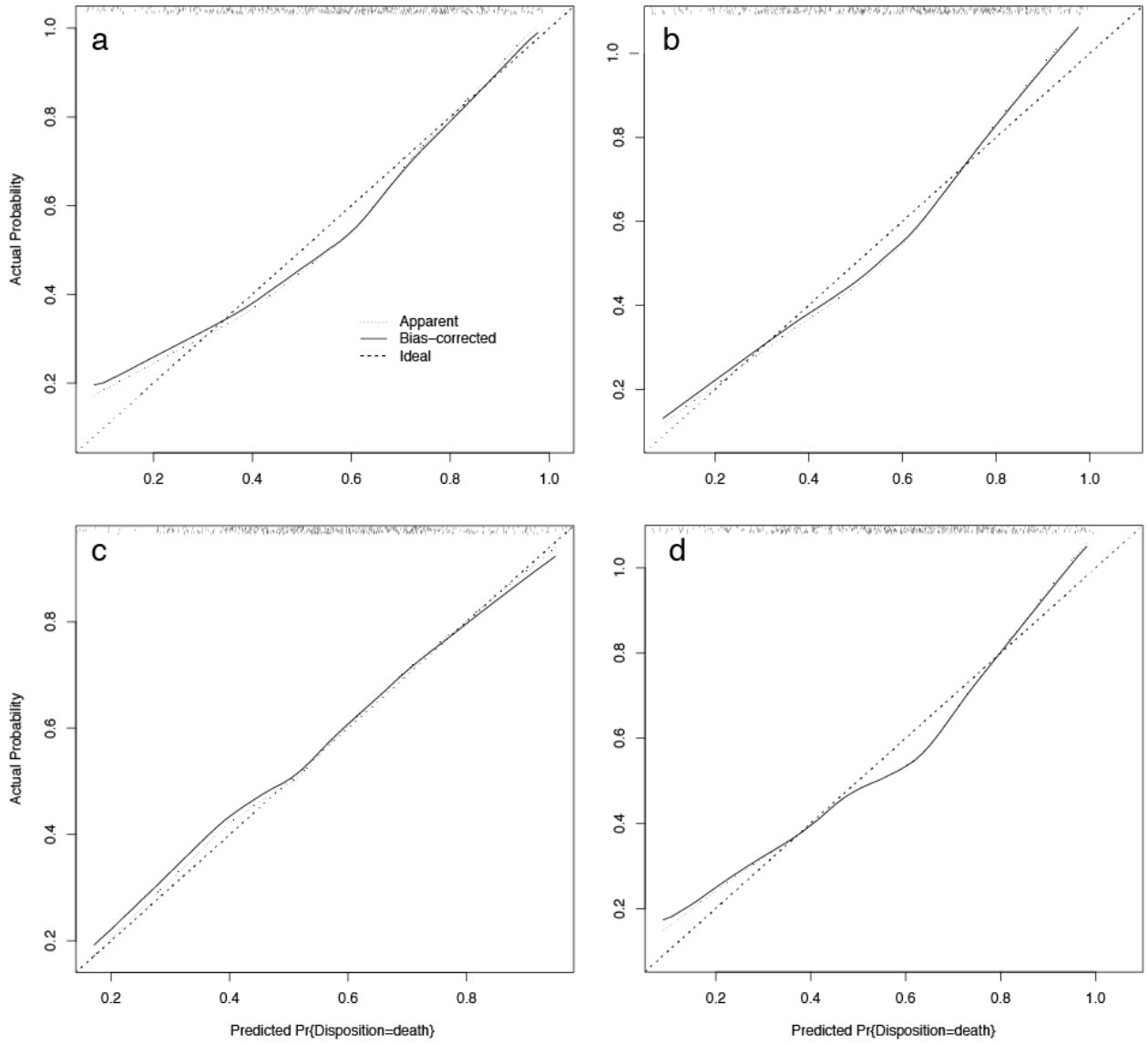

Figure 3. Bootstrap overfitting-corrected calibration curves for the wellness models. Estimated for the four prognostic models using the wellness scale as predictor: wellness+lab (a), wellness+lab without malaria (b), wellness clinical-only (c), and wellness minimal (d)

Ebola Care Guidelines App

We developed a mobile app for Android mobile devices that integrates patient data with the prognostic models and a custom severity score visualization. This app only requires internet connectivity to be installed the first time, and it can be used even when the device is offline afterwards. This is an important consideration as Ebola health workers are often deployed in rural or remote locations with limited internet access. The choice of the Android OS was also informed by the increasing adoption of affordable Android smartphones in low- and medium-income countries in Africa and elsewhere. The home screen of the app shows a list of supportive care recommendations for Ebola fever patients, compiled from Lamontagne et al. (9), WHO and MSF's care and management guidelines for hemorrhagic fevers, and UpToDate's treatment and prevention guidelines for Ebola virus disease (Figure 4A). The list is categorized by intervention type (such as oral rehydration, parenteral administration of fluids, monitoring of viral signs and volume status, etc.). Selecting a recommendation from this list provides a summary description and specific interventions related to that recommendation (Figure 4B), obtained from WHO's manual for the care and management of patients in Ebola Care Units/Community Care Centers (32) and MSF's clinical management of patients with viral hemorrhagic fever pocket guide for front-line health workers (33). These documents are also available in their complete form from the app. When users select a specific intervention, the app redirects to the corresponding page in the document (Figure 4C) but they can also browse into other sections. Accessing this information does not require entering any patient data; in this way the app can be useful simply as a targeted entry point to these detailed guidelines.

Users can also input patient information (age, sex, pregnancy status, weight, height), clinical signs and symptoms recorded at triage, laboratory results from the first RT-PCR and malaria test conducted after admission into the ETU, and the wellness scale (WS) from the first clinical rounds after admission. The app provides a built-in data entry form for this purpose (Figure 4D), or it can be connected to a CommCare app to retrieve the patient information. After all, or some, of this information is recorded, the app uses it to computes the severity score of the patient by selecting the appropriate model for the available indicators. The app offers a visualization of the score and the magnitude of patient-specific contributions for each feature included in their score, where the score value is shown at the top in a color-graded scale and patient-specific feature contributions to that score are depicted in a bar chart summary page (Figure 4E).

Each clinical feature is linked to one or more care recommendations, so that when that feature is present in the data, the corresponding recommendation is highlighted (Figure 4F). The total severity score can also be linked to specific recommendations when it is over a threshold defined in the app's settings. Those recommendations will also be highlighted when the score is higher than the selected threshold. This feature is designed to bring the user's attention to the recommendations that could be most relevant given the clinical manifestation of the patient.

Figure 4. Ebola Care Guidelines app. The home screen presents the list of recommendations (A), which can be selected to access specific interventions associated to each recommendation (B). Selecting a specific intervention or guideline redirects the user to the corresponding section in the WHO's manuals

for care and management of hemorrhagic fever patients (C). The app allows the users to enter basic demographic information (age, weight), vitals, signs & symptoms at presentation, lab data (CT value from first RT-PCR and malaria test result), and wellness scale (D). Based on the available data, the app calculates the severity score of the patient using the suitable prognostic model and presents a customized risk visualization (E). The recommendations that are associated with the presentation signs and symptoms are highlighted in the home screen (E).

Discussion

The purpose of this study was two-fold: first, to present multivariate EVD prognostic models derived from the largest multi-center clinical dataset available to date, externally validated across diverse sites representing various periods of the largest Ebola epidemic on record; and second, to show how these models could guide clinical decisions by organizing existing knowledge of patient care and management more efficiently and making it easily available as a mobile app. The IMC models recapitulate several findings reported earlier in the literature and also reveal further associations between mortality and clinical signs/symptoms. While the occurrence of jaundice or bleeding at initial presentation are important predictors of death, both have low incidence at triage among the patients in the IMC cohort of only 5%. In contrast, more widespread EVD manifestations such as confusion and weakness have a much weaker correlation with mortality, at least based on their presence at triage, which seems to suggest that presentation of these clinical features says little about the clinical evolution of the patient.

In order to account for different levels of clinical detail collected at the ETUs, we constructed a family of prognostic models that range from models requiring only clinical signs/symptoms or age and viral load, to more complex models incorporating a mixture of laboratory data, signs/symptoms, and even observational assessments from experienced health providers. The discriminative capacity of these models is robust across the training set and two independent testing sets, which were obtained at distinct times during the epidemic, with AUCs ranging from 0.75 up to 0.8. While the most informative descriptors for predicting EVD outcome are patient age and viral load, more complex models offer higher accuracy by covering a larger proportion

of the cohort. Inclusion of additional predictors in the models, even those weakly associated with the outcome, result in increased performance and improved stratification of observed patient outcomes. Our parsimonious model, incorporating several clinical signs/symptoms available at initial presentation – fever temperature, jaundice, bleeding, weakness, confusion, breathlessness – in addition to the viral load and malaria test result, performs well on two independent datasets used for external validation. These datasets have a wide temporal, geographic and clinical scope. A major difference between these datasets was the time during which they were collected, with the KGH data representing an earlier time point, with less refined treatment protocols, higher viral virulence, increased patient volume and admission intensity with a larger number of patients delayed during transfers from holding centers. On the other hand, the GOAL dataset includes patients from the final months of the epidemic with a 13% lower CFR. Thus, as may be expected, the models underestimated the observed risk for patients of the KGH cohort, while observed risk was slightly overestimated in the GOAL cohort. The IMC training dataset covers a much broader temporal window of the epidemic as well as a wider catchment area, spanning several districts across two countries, which may explain its robust performance in these disparate populations.

Despite being the largest EVD prognosis modeling study to date, the amount and quality of available clinical data is still limited. We accounted for these limitations by applying various statistical techniques recommended for prognosis modeling (multiple imputation, bootstrap sampling, external validation), but ultimately future predictive models will require larger and better datasets. Indeed, we have integrated machine learning capability into our models specifically to respond to this limitation, allowing our models to be updated with new data. For

the current models, we adapted the available information to extract the most value from the dataset, for example, in order to increase CT data, we aggregated measurements from different PCR labs, despite the use of different assays. Clinical signs/symptoms might be affected by variations in clinical assessments from the multitude of clinicians with varying levels of experience, and errors in data collection (including patient symptom recall or history taking skills). The performance of models incorporating the clinical wellness score is at least comparable or superior to the more detailed models including individual clinical features deemed as the most predictive in our variable selection process. This is in fact a very important result in our study, since it suggests that machine learning approaches, when properly designed and implemented, and applied on rich-enough data, could approximate the clinical intuition that physicians acquire through their experience in the field. One conclusion that can be derived from this is that these models may be useful in emergency situations when the appropriate experience is unavailable or under-developed. Obviously, good quality data is a pre-requisite to construct these models, which is often a challenge in the context of neglected tropical diseases. Thus, prediction models need to be coupled with systematic and standardized data collection systems such as what is provided by our mobile application. Teaming this up with machine learning allows the systematically accumulating data to mature and evolve into more precise predictions.

Finally, with the Ebola Care Guidelines app we aimed at developing a robust system that clinicians can trust in the field and in emergency situations. An initial step in that direction is to complement the prognosis predictions with authoritative clinical care information provided by sources such as the WHO. In this way, we envision the app both as a reference tool to improve training and adherence to protocol, as well as a support system that organizes clinical procedures

more effectively around the patient's data. The integration of mHealth platforms with rapid point of care diagnostic kits (34, 35) has the potential to realize the concept of a “pocket lab” (36), which could be used outside laboratory settings and during health emergencies. The ultimate goal of these platforms is to aid clinical management decisions on the ground by enabling the design of clinical support systems for front-line workers that better organize and provide access to the existing medical knowledge on viral hemorrhagic fevers. The usefulness of such systems would be even larger if they were available not only as stand-alone apps, but could also be integrated with existing data collection platforms, such as CommCare, REDCap, and Open Data Kit. These platforms have been used to launch many successful health programs around the world (37-42). This is why we implemented our app in such a way that it can be embedded into a CommCare app for field data collection. The clinical guidelines are then tailored to reflect the patient’s clinical signs, symptoms and laboratory results. Our approach is generalizable in the sense that it can be applied to create new mobile apps for other tropical diseases affecting rural and low-resource areas, and also provides a mechanism to keep the clinical guideline apps updated as the medical knowledge is refined, and more accurate prognostic models are developed in the light of new and better data. We believe that if clinical staff can obtain actionable information from these data-derived tools, then they may be incentivized to generate more and higher-quality data, which could then be incorporated back into the models, creating a positive feedback loop which drives increased precision. Further, the visualization of the clinical make up of prediction models (such as is provided in this application) provides a learning platform that builds informed clinical experience rather than simply replacing it. The use of low-cost tools on the ground, in combination with effective data collection and sharing among all

stakeholders, will be key elements in the early detection and containment of future outbreaks of Ebola and other emerging infectious diseases.

Availability of source code, data, and app

The source code of all the modeling steps, from parameter fitting to internal and external validation, is openly available as a fully documented Jupyter notebook, deposited online at https://github.com/broadinstitute/ebola-imc-public. Refer to IMC's Ebola Response page (https://internationalmedicalcorps.org/ebola-response), for instructions on how external researchers can access the data. The app is freely available on Google Play: https://play.google.com/store/apps/details?id=org.broadinstitute.ebola_care_guidelines. To enable data entry using CommCare, please contact Dr. Andres Colubri (andres@broadinstitute.org).

Acknowledgments

We would like to thank the governments of Liberia, Sierra Leone, and Guinea for contributing to International Medical Corps' humanitarian response. We would also like to thank all of our generous institutional, corporate, foundation, and individual donors who placed their confidence and trust in International Medical Corps and made our work during the Ebola epidemic possible. We would also like to thank the United States Naval Medical Research Center, Public Health England, the European Union Mobile Laboratory, and the Nigerian Laboratory for providing laboratory data to our Ebola Treatment Units. We would like to further acknowledge all members of our Research Review Committee and other technical teams that contributed to this research. Finally, we would also like to thank our clinical, WASH, and psychosocial teams as well as all of our monitoring and evaluation staff, including the data collection officers at each of our ETUs. AC would like to thank Mary Lynn Baniecki and Christian Matranga for insightful discussions on the EBOV qPCR assays, and Christopher Moxon for critical feedback on the manuscript. Finally, we thank the patients included in this study whose data has and will continue to make invaluable contribution to improving future Ebola care.

References

1. Barry A, Ahuka-Mundeke S, Ali Ahmed Y, Allarangar Y, Anoko J, Archer BN, et al. Outbreak of Ebola virus disease in the Democratic Republic of the Congo, April–May, 2018: an epidemiological study. The Lancet. 2018;392(10143):213-21.

2. CDC. 2018 Eastern Democratic Republic of the Congo 2018 [Available from: https://www.cdc.gov/vhf/ebola/outbreaks/drc/2018-august.html.

3. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). The Lancet. 2017;389(10068):505-18.

4. Amarasingham R, Patel PC, Toto K, Nelson LL, Swanson TS, Moore BJ, et al. Allocating scarce resources in real-time to reduce heart failure readmissions: a prospective, controlled study. BMJ Quality & Safety. 2013;22(12):998-1005.

5. Mitchell M, Hedt-Gauthier BL, Msellemu D, Nkaka M, Lesh N. Using electronic technology to improve clinical care – results from a before-after cluster trial to evaluate assessment and classification of sick children according to Integrated Management of Childhood Illness (IMCI) protocol in Tanzania. BMC Medical Informatics and Decision Making. 2013;13(1):95.

6. Lund S, Boas I, Bedesa T, Fekede W, Nielsen H, Sørensen B. Association between the safe delivery app and quality of care and perinatal survival in ethiopia: A randomized clinical trial. JAMA Pediatrics. 2016;170(8):765-71.

7. Colubri A, Silver T, Fradet T, Retzepi K, Fry B, Sabeti P. Transforming Clinical Data into Actionable Prognosis Models: Machine-Learning Framework and Field-Deployable App to Predict Outcome of Ebola Patients. PLoS neglected tropical diseases. 2016;10(3):e0004549.

8. Schieffelin JS, Shaffer JG, Goba A, Gbakie M, Gire SK, Colubri A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med. 2014;371(22):2092-100.

9. Lamontagne F, Fowler RA, Adhikari NK, Murthy S, Brett-Major DM, Jacobs M, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. The Lancet. 2018;391(10121):700-8.

10. Hunt L, Gupta-Wright A, Simms V, Tamba F, Knott V, Tamba K, et al. Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study. The Lancet Infectious Diseases. 2015;15(11):1292-9.

11. Zhang X, Rong Y, Sun L, Liu L, Su H, Zhang J, et al. Prognostic Analysis of Patients with Ebola Virus Disease. PLoS neglected tropical diseases. 2015;9(9):e0004113.

12. Yan T, Mu J, Qin E, Wang Y, Liu L, Wu D, et al. Clinical characteristics of 154 patients suspected of having Ebola virus disease in the Ebola holding center of Jui Government Hospital in Sierra Leone during the 2014 Ebola outbreak. Eur J Clin Microbiol Infect Dis. 2015:1-7.

13. Li J, Duan H-J, Chen H-Y, Ji Y-J, Zhang X, Rong Y-H, et al. Age and Ebola viral load correlate with mortality and survival time in 288 Ebola virus disease patients. International Journal of Infectious Diseases. 2016;42:34-9.

14. Crowe SJ, Maenner MJ, Kuah S, Erickson BR, Coffee M, Knust B, et al. Prognostic Indicators for Ebola Patient Survival. Emerging Infectious Disease journal. 2016;22(2):217.

15. Steyerberg EW, Moons KGM, van der Windt DA, Hayden JA, Perel P, Schroter S, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. PLOS Medicine. 2013;10(2):e1001381.

16. Goldstein BA, Navar AM, Pencina MJ, Ioannidis JP. Opportunities and challenges in developing risk prediction models with electronic health records data: a systematic review. Journal of the American Medical Informatics Association. 2016.

17. Hartley M-A, Young A, Tran A-M, Okoni-Williams HH, Suma M, Mancuso B, et al. Predicting Ebola Severity: A Clinical Prioritization Score for Ebola Virus Disease. PLoS neglected tropical diseases. 2017;11(2):e0005265.

18. Roshania R, Mallow M, Dunbar N, Mansary D, Shetty P, Lyon T, et al. Successful Implementation of a Multicountry Clinical Surveillance and Data Collection System for Ebola Virus Disease in West Africa: Findings and Lessons Learned. Global Health: Science and Practice. 2016;4(3):394-409.

19. Harrell FE. Regression modeling strategies : with applications to linear models, logistic and ordinal regression, and survival analysis. Second edition. ed. Cham: Springer; 2015. 1 online resource (xxv, 582 pages) p.

20. Saar-Tsechansky M, Provost F. Handling Missing Values when Applying Classification Models. J Mach Learn Res. 2007;8:1623-57.

21. Hartley M-A, Young A, Tran A-M, Okoni-Williams HH, Suma M, Mancuso B, et al. Predicting Ebola infection: A malaria-sensitive triage score for Ebola virus disease. PLoS neglected tropical diseases. 2017;11(2):e0005356.

22. Gire SK, Goba A, Andersen KG, Sealfon RSG, Park DJ, Kanneh L, et al. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science (New York, NY). 2014;345(6202):1369-72.

23. Center USNMR. Ebola Zaire (EZ1) rRT-PCR (TaqMan) Assay. 2014.

24. Trombley AR, Wachter L, Garrison J, Buckley-Beason VA, Jahrling J, Hensley LE, et al. Comprehensive Panel of Real-Time TaqMan™ Polymerase Chain Reaction Assays for Detection and Absolute Quantification of Filoviruses, Arenaviruses, and New World Hantaviruses. The American journal of tropical medicine and hygiene. 2010;82(5):954-60.

25. Prevention CfDCa. Ebola Virus VP40 Real-Time RT-PCR Assay. 2014.

26. Van Belle V, Van Calster B. Visualizing Risk Prediction Models. PloS one. 2015;10(7):e0132614.

27. Schieffelin J, Shaffer J, Goba A, Gbakie M, Gire S, Colubri A, et al. Clinical Illness and Outcomes in Patients with Ebola in Sierra Leone. The New England journal of medicine. 2014.

28. de La Vega M-A, Caleo G, Audet J, Qiu X, Kozak RA, Brooks JI, et al. Ebola viral load at diagnosis associates with patient outcome and outbreak evolution. The Journal of Clinical Investigation. 2015;125(12):4421-8.

29. Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections. New England Journal of Medicine. 2014;371(16):1481-95.

30. Barry M, Traoré FA, Sako FB, Kpamy DO, Bah EI, Poncin M, et al. Ebola outbreak in Conakry, Guinea: Epidemiological, clinical, and outcome features. Médecine et Maladies Infectieuses. 2014;44(11):491-4.

31. Qin E, Bi J, Zhao M, Wang Y, Guo T, Yan T, et al. Clinical Features of Patients With Ebola Virus Disease in Sierra Leone. Clinical Infectious Diseases. 2015;61(4):491-5.

32. WHO. Manual for the care and management of patients in Ebola care units / Community Care Centres: interim emergency guidance, January 2015. 2015.

33. WHO. Clinical management of patients with viral haemorrhagic fever. A pocket guide for front-line health workers. 2016.

34. Broadhurst MJ, Kelly JD, Miller A, Semper A, Bailey D, Groppelli E, et al. ReEBOV Antigen Rapid Test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study. The Lancet.386(9996):867-74.

35. Yen C-W, de Puig H, Tam JO, Gomez-Marquez J, Bosch I, Hamad-Schifferli K, et al. Multicolored silver nanoparticles for multiplexed disease diagnostics: distinguishing dengue, yellow fever, and Ebola viruses. Lab on a Chip. 2015;15(7):1638-41.

36. Radin JM, Topol EJ, Andersen KG, Steinhubl SR. A laboratory in your pocket. The Lancet.388(10054):1875.

37. Sacks JA, Zehe E, Redick C, Bah A, Cowger K, Camara M, et al. Introduction of Mobile Health Tools to Support Ebola Surveillance and Contact Tracing in Guinea. Global Health: Science and Practice. 2015;3(4):646-59.

38. Balakrishnan R, Gopichandran V, Chaturvedi S, Chatterjee R, Mahapatra T, Chaudhuri I. Continuum of Care Services for Maternal and Child Health using mobile technology – a health system strengthening strategy in low and middle income countries. BMC Medical Informatics and Decision Making. 2016;16(1):84.

39. Kaphle S, Chaturvedi S, Chaudhuri I, Krishnan R, Lesh N. Adoption and Usage of mHealth Technology on Quality and Experience of Care Provided by Frontline Workers: Observations From Rural India. JMIR mHealth uHealth. 2015;3(2):e61.

40. Cherutich P, Golden M, Betz B, Wamuti B, Ng'ang'a A, Maingi P, et al. Surveillance of HIV assisted partner services using routine health information systems in Kenya. BMC Medical Informatics and Decision Making. 2016;16(1):97.

41. Steiner A, Hella J, Grüninger S, Mhalu G, Mhimbira F, Cercamondi CI, et al. Managing research and surveillance projects in real-time with a novel open-source management tool designed for under-resourced countries. Journal of the American Medical Informatics Association. 2016;23(5):916-23.

42. Tom-Aba D, Olaleye A, Olayinka AT, Nguku P, Waziri N, Adewuyi P, et al. Innovative Technological Approach to Ebola Virus Disease Outbreak Response in Nigeria Using the Open Data Kit and Form Hub Technology. PloS one. 2015;10(6):e0131000.