Development of the PREDS score to predict in-hospital mortality of patients with Ebola virus disease under advanced supportive care: Results from the EVISTA cohort in the Democratic Republic of the Congo

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Summary

Background As mortality remains high for patients with Ebola virus disease (EVD) despite new treatment options, the ability to level up the provided supportive care and to predict the risk of death is of major importance. This analysis of the EVISTA cohort aims to describe advanced supportive care provided to EVD patients in the Democratic Republic of the Congo (DRC) and to develop a simple risk score for predicting in-hospital death, called PREDS.

Methods In this prospective cohort (NCT04815175), patients were recruited during the 10th EVD outbreak in the DRC across three Ebola Treatment Centers (ETCs). Demographic, clinical, biological, virological and treatment data were collected. We evaluated factors known to affect the risk of in-hospital death and applied univariate and multivariate Cox proportional-hazards analyses to derive the risk score in a training dataset. We validated the score in an internal-validation dataset, applying C-statistics as a measure of discrimination.

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Findings Between August 1st 2018 and December 31th 2019, 711 patients were enrolled in the study. Regarding supportive care, patients received vasopressive drug (n = 111), blood transfusion (n = 101), oxygen therapy (n = 250) and cardio-pulmonary ultrasound (n = 15). Overall, 323 (45%) patients died before day 28. Six independent prognostic factors were identified (ALT, creatinine, modified NEWS2 score, viral load, age and symptom duration). The final score range from 0 to 13 points, with a good concordance (C = 86.24%) and calibration with the Hosmer-Lemeshow test (p = 0.12).

Interpretation The implementation of advanced supportive care is possible for EVD patients in emergency settings. PREDS is a simple, accurate tool that could help in orienting early advanced care for at-risk patients after external validation.

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Keywords: Ebola virus; Sub-Saharan Africa; Supportive care; Outcome; Predictive score; In-hospital mortality

Research in context

Evidence before this study

Mortality from Ebola virus disease (EVD) remains a major issue, despite the development of new specific treatments. Advanced supportive care and early detection of severe cases are levers that could further reduce mortality. We search Pubmed from January 1st 2014 to July 1st 2022 for cohorts related to intensive care in EVD patients on low-resource settings. The search was done with no language restriction and using the search terms "Ebola virus", "West Africa", "Guinea", "Sierra Leone", "Liberia", "Democratic Republic of the Congo" and "intensive care" in titles and abstracts. Advance supportive care were already provided to EVD patients in Sierra Leone in an Ebola treatment center (ETC) equipped with intensive care unit on a small number of patients in comparison with "regular ETC". Access to intensive care was then associated with lower mortality. In addition, several article highlight the urgent need to scale up the level of supportive care to improve mortality.

We did a similar search for articles related to the development or validation of prognostic models for in-hospital death (search terms "prognostic", "death", "outcome", "score"). Two scores were developed using clinical, socio-demographics, or virological data from the Sierra Leone 2014–2015 outbreak data but were not internally or externally validated and did not include biological variables. Furthermore, the clinical relevance and feasibility of these two scores is debatable. One score includes a lot of clinical variables, including socio-demographic variables whose association with mortality is not obvious, with no biological variables, while the other includes very few variables, with no biological considerations either. The scoring of EVD severity remains then a key question in order to orientate rapidly patients in in advanced care unit.

Added value of this study

We collected clinical, biological, and virological data on all patients attending to the three ETCs providing advanced supportive care and investigational treatments during the 10th outbreak in the DRC. With these data, we were able to develop a prognostic score model that predicts the day 28 in-hospital risk of death of EVD patients.

Implication of all the available evidence

This cohort has demonstrated that access to optimized supportive care can be offered during EVD outbreaks even in low-resource settings. After being externally validated, early triage using our prognostic score may help rapid identification of at-risk patients in order to provide EVD patients with adapted critical care.

Introduction

The Ebola virus disease (EVD) outbreak in the Democratic Republique of the Congo (DRC) that occurred between August 2018 and June 2020 involved 3,470 cases and resulted in 2287 deaths. It affected three provinces in the east of the country (Ituri, North Kivu and South Kivu).[1] After being validated in the 2014–2016 West African outbreak, the specific Ebola Virus (EBOV) vaccine (r-VSV-ZEBOV, ERVEBO, Merck) was used for ring vaccination of contacts and contacts of contacts.[2,3] In addition, during this DRC 10th outbreak, a specific treatment was identified. The MEURI (Monitored Emergency Used for Unregistered Intervention) and the PALM trials evaluated 3 investigational drugs, two of them showed efficacy in term of mortality improvement: REGN-EB3and MAb114 (monoclonal antibody products).[4]

Even using these treatment strategies, the mortality remains high for severe cases.[4] Thus, any strategy that

can help reduce mortality should be explored. We provide in this paper two leads that could help in future outbreaks: advanced supportive care and early triage of at-risk patients.

Supportive care is an important therapeutic strategy.[5–10] However, the precise spectrum of supportive care is wide and there is no clear indication as to its application, as it depends on a combination of several complicated actions.[11] The spectrum of supportive care therefore requires definition in order to optimize its feasibility in the field.

Early triage of patients also remains of prime importance in reducing mortality rates. Understanding which patients are more at risk of death and have the highest chance of being saved is a crucial issue to address.

The present study set out to describe the supportive care provided to patients during the 10th Ebola outbreak in the DRC, and to develop an individual death risk score model, herein referred to as PREDS (PRedicting Ebola Death risk Score).

Methods

Participants and setting

Within the context of the operational response to Ebola outbreaks in the DRC, the national Ministry of Health, with the support of the French NGO ALIMA (Alliance for International Medical Action), has established three Ebola Treatment Centers (ETCs) in the North Kivu and Ituri provinces, at the Beni, Katwa and Mambassa urban centers.

EVISTA (Ebola Virus STAndard of care) is an observational cohort set up for the duration of the outbreak, with the aim of describing the standard of care provided to Ebola patients, and the clinical and biological course of the disease. All patients with a positive EBOV RT-PCR test admitted to an ETC during the inclusion period were included. Patients were followed from admission until discharge or death in ETC.

Care, treatment and follow-up

All EVD patients received a standard of care in accordance with the DRC Ministry of Health recommendations and WHO guidelines.[11] Clinical evaluation was carried out using a modified version of the NEWS2 (mNEWS2) score without the respiratory rate, for practical reasons (Figure S4).[12] Advanced supportive care tools were used to improve clinical management. Four investigational drugs were available through PALM or MEURI (Remdesivir, REGN-EB3, Zmapp and MAb11). Follow-up was similar during PALM and MEURI. An innovative measure, the Biosecure Emergency Room (BER), was developed to treat cases in individual spaces within the units.[5,13,14] Haemotological, biochemical, and virological analysis were done in each ETC (more detail on the devices available in annex 4).

Data collection

Data regarding the demographic and clinical situations, biological parameters and medication received were collected for all patients at admission. The outcome and a summary of the hospitalization were collected at discharge or death. Data regarding vaccination status were based on patient declaration.

Statistical analysis

Baseline characteristics, follow-up supportive care, treatment, and observed outcomes were summarized using median and interquartile range (IQR) for continuous variables, and count and percentage for categorical variables. Statistical comparisons were carried out using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables. Time-to-event was estimated as the period from date of admission to date of death for the patients who died. Patients who survived the whole study period ceased to be monitored at the end of their follow-up period, i.e. day 28. Univariate Cox proportional hazard regression models were used to assess the association of key baseline characteristics with risk of death for all patients.

Prognostic model development

The selection of candidate predictors included in the model was based on the literature, the results from the univariate Cox models, and input from clinical experts. Three multivariable Cox proportional hazard model were explored: one full model (i.e. with all candidate predictors), and two least absolute shrinkage and selection operator (LASSO) models. The outcome was death before day 28 after admission. To develop and validate the PREDS score, patients with non-missing data on all candidate predictors and the outcome were randomly allocated to either a training sample (2/3 of the data) or a validation sample (1/3 of the data). The training sample was used to develop and parametrize the prediction model, and the validation sample was used to test out-of-sample prediction model performance. Predictive performance was assessed in the validation set by 1) model concordance, measured by the C-statistic, and 2) model calibration for risk of death at 28 days, quantified by the Hosmer-Lemeshow goodness-of-fit test. The Breslow estimator of the baseline hazard was combined with the HRs to obtain the predicted risk of death for each patient at 28 days from admission date.

Prognostic score development

PREDS was developed as a simple points-based system to characterize patient risk scores using the methods of Sullivan and D'Agostino.[15] Creatinine was categorized according to a clinically relevant cut-off, and a reference value operationalized as the midpoint was calculated using the 1st and 99th percentile values to minimize the

influence of extreme values. A base risk profile was set to correspond to the lowest risk category for each variable. The constant for the points system (number of regression units corresponding to one point) was defined as the increase in risk associated with a 2-unit (mg/dL) increase in creatinine. Factor states associated with a higher risk of death were assigned more points, so a higher points total represented greater risk. The points for each predictor were totaled, and a table indicating risk (defined as the probability of dying within 28 days of admission) for each points total was established.

Prognostic score internal validation

To evaluate the robustness of the risk-scoring algorithm, the points system based on the training sample was used to generate risk scores for patients in the validation sample, and the correlation between the points-based risk scores and the Cox model-based risk scores was assessed. To evaluate the impact of missing data, a sensitivity analysis was carried out to assess the model's predictive performance in multiple imputed held-out (i.e., validation) datasets. This approach allowed the robustness of the prediction model to be evaluated across a range of imputed datasets to assess how well the model would perform in other datasets with no missing data. Multiple imputation was carried out using the multivariate imputation by chained equations (MICE) approach,[16] which has been the preferred approach for handling missing data based on published simulation studies.[17] In this analysis, 200 validation imputations were generated. Then, model concordance C-statistic, *p*-value for the Hosmer–Lemeshow goodness-of-fit test, and correlation coefficient between points-predicted risk and model-predicted risk were obtained for each imputed validation set. The mean values across all 200 validation sets were then calculated and compared with the respective values obtained in the non-imputed (empirical) validation set.

All statistical analyses were performed with the R statistical package version 4.0.3 or later (R Foundation for Statistical Computing). The results were reported following the TRIPOD statement (supplementary material).

Ethical consideration

The consent of patients included in the cohort was (i) extrapolated from their signed consent to participation in the RCT or MEURI studies (the data collected were part of the medical support we had provided for these patients) or (ii) collected through specific consent forms for EVISTA. For patients unable to sign the consent form, relatives were contacted to sign for them. The EVISTA protocol was approved by the DRC National Ethics Committee (151/CNES/BN/PMMFI2019) and registered with clinicaltrial.gov (NCT04815175).

Role of funding sources

The funding sources took no part in designing the study, collecting, analyzing or interpreting the data, writing the report or making the decision to submit the article for publication.

Results

Description of the cohort (Table 1 and S1)

Between August 1st 2018 and December 31th 2019, 711 patients were eligible for analysis (Figure 1). The mean (± SD) age was 28 (± 17) years. Patients were admitted at a median of 4 days from onset of symptoms. In terms of vaccination status, 175 (33%) declared they had been vaccinated with the rVSV-ZEBOV-GP vaccine. Of the 134 patients who reported their vaccination date, 93 had been vaccinated 10 days or less before admission (median 7 days, IQR 5-8), and 41 more than 10 days before admission (median 15 days, IQR 12-41). Biological parameters at baseline (Table S2) showed a low platelet count in 158 patients (54%), a high white blood cell count in 138 (46%), and an increased level of creatinine in 271 (49%). The CRP value was above 5 mg/l for 512 patients (99%). Serum sodium was low (<130mmol/l) for 183 patients (33%) and 166 (35%) had an abnormal level of potassium. Values for AST and ALT were more than 5 times the upper limit for normal rang in 224 (59%) and 262 patients (48%) respectively. The albumin level was low (≤ 35 g/l) in 490 patients (88%). In terms of viral load measurement, the EBOV RT-PCR NP Ct value was ≤ 22 for 356 patients (54%), while the GP Ct value was ≤ 22 for only 83 patients (13%).

Follow-up (Table S1)

Almost all patients (94%) experienced viral-illness-like symptoms such as fatigue (91%), anorexia (70%) and headache (57%). Half of them showed respiratory symptoms and a critical oxygen saturation below 92%. In addition, 86% of patients had digestive symptoms, of which 75% diarrhea and 34% dysphagia. A total of 238 patients (35%) experienced an impaired level of consciousness (CVPU on the ACVPU scale) and 264 (37%) had no neurological symptoms. The most common neurological symptoms were agitation and coma (in 25% and 29% of patients respectively). 103 patients (15%) experienced seizure during follow-up. Overall, 275 patients (39%) had bleeding symptoms of some type, the most common being venous puncture point bleeding, melena, gingival bleeding and hematemesis (20%, 14%, 12% and 11% respectively).

Investigational treatment and patient care

Overall, 623 patients (88%) were given an investigational treatment, 453 (73%) in the context of PALM and 170 (27%) in MEURI. Most patients were managed in

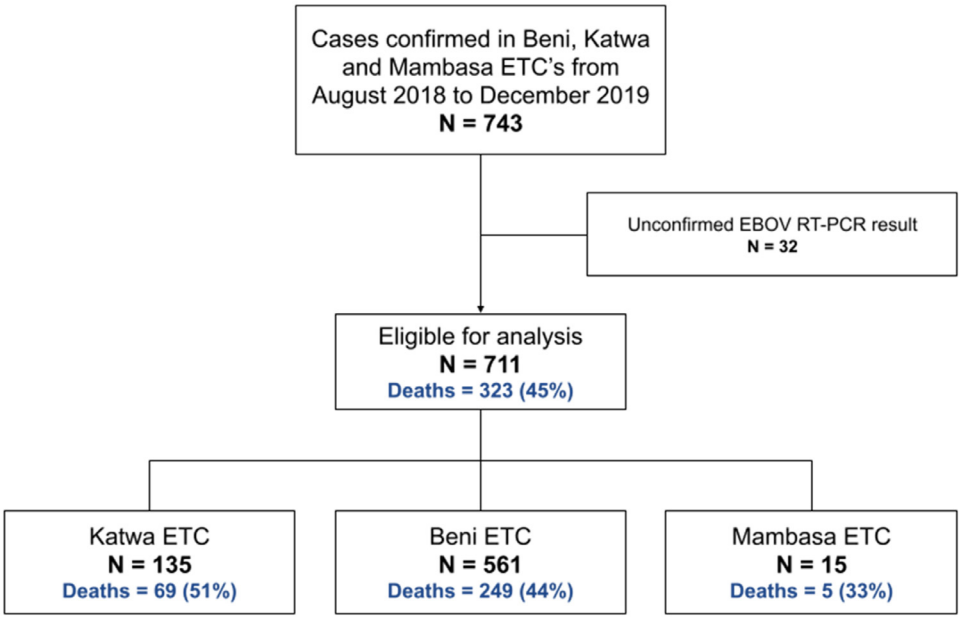

Figure 1. Inclusion flowchart.

the BER from the time of admission, mainly for biosafety reasons. All the supportive interventions provided to the patients are detailed in Table 2.

Outcomes

Of the 711 patients involved, 323 (45%) died after a median of 2 days (IQR 1-5) from admission and 9 days (IQR 6-12) from onset of symptoms (Table 2). In addition, lethality dropped to 36% and 29% in patients hospitalized for more than 24 h and 48 h respectively.

The case fatality rate (CFR) was 39% (243/623) among the patients who received an investigational treatment, and 91% (79/87) among those who did not (64 of them could not receive it because they died before having the possibility to receive the treatment, within the first 24 h of admission). The CFR of the 175 patients who declared being vaccinated was 30% (vs. 49% for unvaccinated). A total of 32 pregnant women and 85 children aged 5 or under were included in the study. Details of the outcomes for these specific groups are given in Figure S1 and table S2 respectively.

Prognostic model development

Six candidate predictors were evaluated: four from the univariate analysis and the literature (ALT, creatinine, mNEWS2 and EBOV RT-PCR), and two from clinical expertise (age and time from 1st symptom to admission, widely used by clinicians on the field to evaluate severity at admission). Some variables were significant at the univariate analysis (table S2) but were not kept to propose a score that is not field dependant (e.g. socio-economic variables), that can be used on resource-limited terrains (e.g. biological variables), and with reliable data (e.g. vaccination). The training sample to develop the prediction model comprised 279 patients randomly selected (Figure 2). Compared to the two LASSO models, prediction performance was similar and calibration at 28 days was better for the full model (i.e. including all candidate predictors). Proportional Hazard was checked graphically and with scaled Schoenfeld residuals (annex 3). The score was developed using this model.

Prognostic score development

The PREDS score was developed by attaching adding points according to the HR of the multivariable Cox model: ALT > 5N (aHR = 2.48 [95%CI 1.46-4.23], 3 points), creatinine > 1.3 mg/dl (aHR = 1.19 [95%CI 1.12 −1.26], 3 points), mNEWS2 score > 4 (aHR = 2.311 [95%CI 1.54−3.48], 2 points), EBOV RT-PCR NP Ct value ≤ 22 (aHR = 2.56 [95%CI 1.56−4.19], 3 points), age ≥ 50 years old (aHR = 1.50 [95%CI 0.89−2.54], 1 point) and time from 1st symptom to admission ≥ 4 days (aHR = 1.44 [95%CI 0.97−2.16], 1 point) (Table 3). The final score ranged from 0 to 13 points, with lower score indicating a lower risk of the outcome. In the internally validated dataset, the estimated risk of death at day 28 ranged from 1.9% (0 point) to 80.8% (13 points) (annex 3). Three risk groups were defined: low (score 0−5, survival probability at D28 92.8% (95%CI 86.3−99.9)), medium (score 6−9, survival probability at D28 53.7% (95%CI 40.4−71.3)), high (score 10−13, survival probability at D28 11.9% (95%CI 5.2−27.1)) (Figure 3).

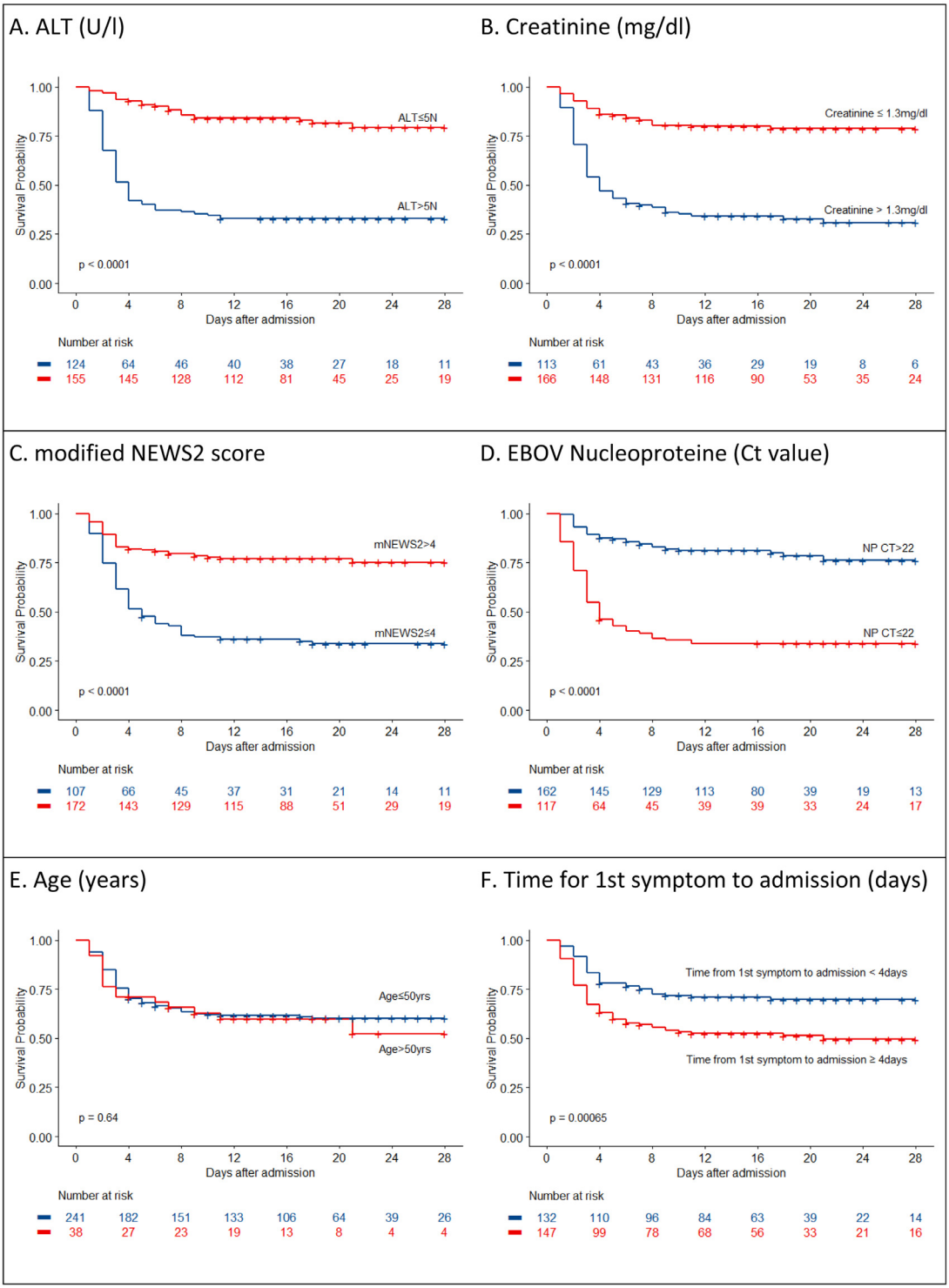

Figure 2. Kaplan Meier probability of death for PREDS individual parameters in the training sample (*N* = 279).

	Value	N
Age, n (%)		676
≤ 5 yr	85 (13%)	
≤ 28 days	6 (1%)	
6 to 18 yr	101 (15%)	
19 to 49 yr	406 (60%)	
≥ 50 yr	84 (12%)	
Sex, n (%)		711
Male	302 (42%)	
Female	409 (58%)	
Positive result on pregnancy test, n (%)	32 (8%)	
Vaccination		
Patient-reported vaccination with rVSV, n (%)	175 (33%)	533
Time from vaccination to admission (days), median [IQR]	8 [5;11]	134
> 10 days before admission, n (%)	41 (31%)	
≤ 10 days before admission, n (%)	93 (69%)	
Time from 1st symptom to admission (days), median [IQR]	4 [2;7]	697
Vital signs, n (%)		
Respiratory rate ≥ 24 breaths per minute	328 (51%)	641
Heart rate ≥ 110 per minute	207 (31%)	666
Diastolic Arterial Pressure < 60 mmHg	134 (23%)	579
Systolic Arterial Pressure < 90 mmHg	89 (15%)	579
SpO2 < 92%	63 (10%)	602
Mean Arterial Pressure < 65 mmHg[a]	49 (8%)	579
Symptoms, n (%)		
Any type of bleeding symptom[b]	123 (17%)	711
Any type of neurologic symptom[c]	99 (14%)	711
Level of consciousness, n (%)		
ACPVU classification:[d]		638
Alert	577 (90%)	
Impaired	61 (10%)	
mNEWS2 score, n (%)[e]		496
Total score ≤ 4	357 (72%)	
Total score > 4	139 (28%)	
Hematology, median [IQR]		
Hemoglobin — g/dl	14 [12;15]	301
Hematocrit — %	40 [36;45]	298
Platelets — G/l	145 [97;222]	294
Leucocytes — G/l	10 [5;21]	300
Lymphocytes — G/l	3 [1;6]	232
Neutrophils — G/l	5 [3;12]	224
Monocytes — G/l	0.4 [0.2;1.0]	222
Renal function, median [IQR]		
Urea — mg/dl	18 [9;48]	553
Creatinine — mg/dl	1.1 [0.7;3.6]	548
Electrolytes and Biochemistry, median [IQR]		
CRP — mg/l	39 [11;109]	517
CPK — U/liter	674 [267;2116]	519
Sodium — mmol/l	131 [128;134]	551
Potassium — mmol/l	4.2 [3.7;4.8]	469
Amylase — U/liter	106 [72;177]	534
Corrected calcemia— mmol/l[f]	2.3 [2.2;2.5]	554
Albumine — g/l	28 [23;33]	556
Glycemia — mg/dl	97 [79;121]	556
Liver function, median [IQR]		
Bilirubin — mg/dl	0.6 [0.5;1.1]	511
ALT — U/liter	212 [60;589]	544
AST — U/liter	292 [93;1018]	378
Virology, n (%)		
EBOV RT-PCR NP Ct value ≤ 22	356 (54%)	655
EBOV RT-PCR GP Ct value ≤ 22	83 (13%)	644

***Table 1*: Baseline characteristics (*N*=711).**

[a] Mean Arterial pressure = 2/3 Diastolic Arterial Pressure + 1/3 Systolic Arterial Pressure.

[b] Epistaxis, hematemesis, hematuria, hemoptysis, melena, purpura, conjunctival bleeding, gingival bleeding, venous puncture point bleeding.

[c] Headache, focal neurological deficit, disorientation/confusion, agitation, convulsions, coma/consciousness disorder, photophobia.

[d] ACVPU classification: A: Alert; C: new confusion; V: responsive to voice; P: responsive to pain, U: Unresponsive.

[e] NEWS2 score: National Early Warning Score 2nd version; mNEWS2: modified NEWS2 score without respiratory rate.

[f] Corrected calcemia = measured calcemia − 0.025*(albuminemia − 40); measured calcemia in mmol/L, albuminemia in g/L.

	Value	N
Supportive care		
Antibiotics, n (%)[a]	636 (100%)	638
Duration (days), median [IQR]	8 [4;14]	
Inotropes, n (%)[b]	111 (16%)	711
Received 1 dose	69 (62%)	
Received 2 doses or more	42 (38%)	
Oxygen therapy, n (%)	250 (38%)	661
Duration (days), median [IQR]	2 [1;3]	188
Highest flow, n (%)		218
< 10 l/min	154 (71%)	
≥ 10 l/min	64 (29%)	
Transfusion, n (%)	101 (14%)	711
Volume (ml), median [IQR]	450 [250;525]	99
Urinary catheter, n (%)	199 (32%)	628
Feeding tubes, n (%)	45 (7%)	654
UltraSound, n (%)	15 (2%)	711
Intraosseus catheter, n (%)	7 (1%)	659
Hospitalized in cube, n (%)	560 (85%)	656
Investigational treatment		
Investigational treatment received, n (%)	623 (88%)	710
Program, n (%)		
MEURI[c]	170 (27%)	
PALM RCT[d]	453 (73%)	
Drugs, n (%)		
MAb114	197 (32%)	

Table 1 (Continued)

Table 2 (Continued)

	Value	N
Regeneron	191 (31%)	
Remdesivir	122 (20%)	
Zmapp	107 (17%)	
Outcome		
Dead, n (%)	323 (45%)	711
Time from admission to death (days), median [IQR]	2 [1;5]	
Alive, n (%)	388 (55%)	711
Time from admission to discharge (days), median [IQR]	17 [14;22]	

***Table 2*: Care, treatment and outcome (*N*=711).**
[a] Ceftriaxone, cefixim, metronidazole, gentamycin, amoxicillin, ciprofloxacin, cloxacillin
[b] Adrenaline, noradrenaline.
[c] Consultation on Monitored Emergency Use of. Unregistered and Investigational Interventions.
[d] Mulangu et al, NEJM, 2019.

Risk factors	Categories	Points
ALT > 5N (U/L)	No	0
	Yes	3
Age (years)	< 50	0
	≥ 50	1
Creatinine (mg/dL)	≤ 1.3	0
	> 1.3	3
Time from 1st symptom to admission (days)	< 4	0
	≥ 4	1
mNEWS2 score > 4	No	0
	Yes	2
EBOV RT-PCR NP Ct value ≤ 22	No	0
	Yes	3
Score category[a]	Low	0–5 Points
	Medium	6–9 Points
	High	10–13 Points

***Table 4*: Points associated with each of the categories of the PREDS score and risk categorization.**
[a] The score is obtained by adding the points obtained by individual risk factors.

Prognostic score validation

The predictive performance of the multivariable Cox model showed good concordance (C = 86.24%) and calibration with the Hosmer- Lemeshow test (p = 0.12) for risk of death at 28 days in the validation sample (Figure S3).

The correlation between points-based risk scores and the Cox model-based risk scores in the validation sample (N = 140) was 93.8%. A plot of the observed survival rates at different time points stratified by predicted risk quartiles (Figure S2) shows that the model-predicted risk scores discriminate well between patient groups with different survival profiles. The sensitivity analyses indicated that the model had a similar predictive value across the 200 multiple imputed held-out datasets. The mean C-statistic (SD) was 82.2% (0.96), compared to 86.2% in the empirical validation set. The mean p-value for the Hosmer–Lemeshow goodness-of-fit test p-value (SD) was 0.09 (0.11), while the corresponding value in the empirical dataset was 0.12. Finally, the mean (SD) correlation coefficient between points-predicted risk and model-predicted risk was 92.7% (0.67), compared to 93.8% in the empirical dataset.

Discussion

This study, characterizing more than 700 patients, represents to our knowledge the largest prospective observational cohort for EVD.

The initial clinical presentation of these patients was similar to that described during the 2014–2016 Ebola outbreak in West Africa.[14,18–22] Likewise,

Risk factor	Prevalence, n%	Hazard Ratio (95% CI)	*P* value	β regression coefficient	Points[b]
ALT > 5N (U/L)	124 (44)	2.48 (1.46, 4.23)	0.0008 *	0.91	3
Creatinine (mg/dL)	-	1.19 (1.12, 1.26) per 1mg/dl increase	<0.0001 *	0.17	3[c]
mNEWS2 score > 4	107 (38)	2.31 (1.54, 3.48)	0.0001 *	0.84	2
EBOV RT-PCR NP Ct value ≤ 22	117 (42)	2.56 (1.56, 4.19)	0.0002 *	0.94	3
Age ≥ 50 years	38 (14)	1.5 (0.89, 2.54)	0.1281	0.41	1
Time from 1st symptom to admission (days) ≥ 4	147 (52)	1.44 (0.97, 2.16)	0.0733	0.37	1

***Table 3*: Multivariate cox proportional-hazards analysis of the training sample and PREDS scoring system (*N*=279)[a].**
[a] The sample size of 279 patients correspond to patients randomly selected from the 711 patients of the cohort with no missing data on all candidate risk factors (i.e. training sample). CI denotes confidence interval, Hazard Ratios for each variable is adjusted on the other variables shown in the table. Crude Hazard Ratios corresponding to the univariate analysis are shown in Table S4.
[b] Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The constant for the points system (number of regression units corresponding to one point) was defined as the increase in risk associated with a 2-unit (mg/dL) increase in creatinine (B=0.34). (cf annex 3).
[c] In the Multivariate Cox Proportional-Hazards Analysis creatinine is used as a continuous variable, but to assign points for the PREDS score it was categorized according to a clinically relevant cut-off (cfTable 4).

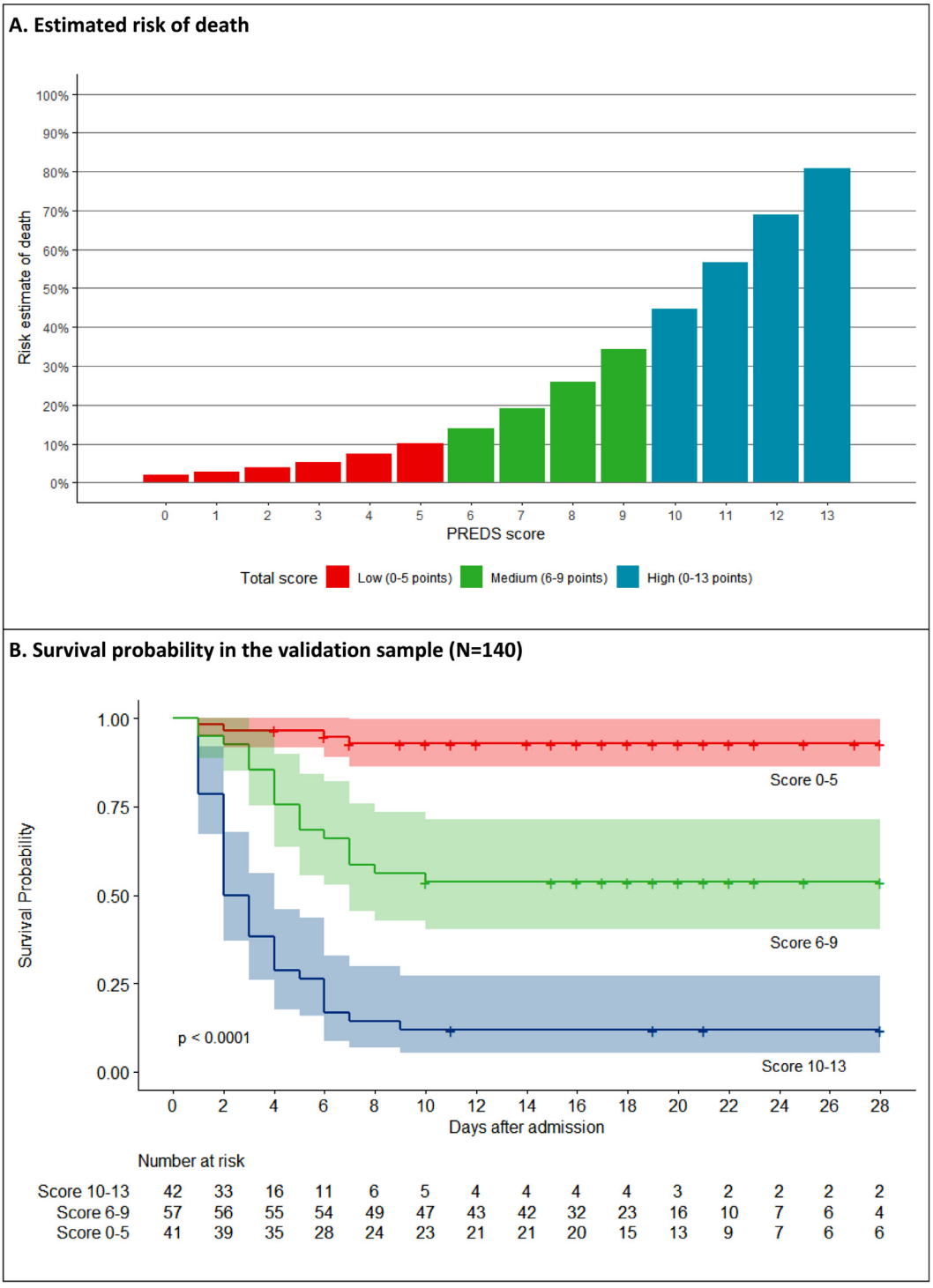

Figure 3. Estimated risk of death and survival probability for a low (Score 0−5), Medium (Score 6−9), or High (Score 10−13) PREDS score.

hyponatremia, renal dysfunction, thrombocytopenia, dyskaliemia and hepatic failure are factors previously described in EVD.[21,23,24] We also recognized that acute renal failure, high viral load, and a high ALT level were indicators of a fatal outcome.[14,23,24] The overall mortality rate for our cohort was 45% - higher than that reported in the PALM trial in which patients with severe symptoms on admission were not included.[4]

Because there have been strong calls for improvements in care standard of care by caregivers,[6–10] symptomatic treatment has improved since the West African epidemic.[9,25] Innovative options such as admission and management in BER, cardiopulmonary ultrasound to guide vascular filling, monitoring of biological parameters allowing the adaptation of electrolyte compensation and oxygen therapy are now available in the field.[5,13] Some patients have even benefited from the placement of a central venous or bone catheter, or treatment with a vasopressive drug to manage cardio-circulatory shock. Specific treatments only have a partial impact on fatality rates in severe patients on admission,[4,26] which is largely supported by the experience of EVD management in northern countries with high levels of supportive care and showing mortality rates of less than 20%, even without specific treatments.[27] The optimization of supportive care should be mandatory in future outbreak management and therefore always involve three elements: (i) very close monitoring of the patient's hydration level (vital constant, electrolytes and possibly cardiopulmonary ultrasound), (ii) early access to oxygen therapy, antibiotics and blood transfusion and (iii) the possibility of advanced resuscitation care such as central catheter placement, dialysis or mechanical ventilation, which could lower fatality rates. The availability of innovative measures such as BERs for severe patients could also help with close monitoring while maintaining biomedical safety for caregivers.[5,13]

However, recourse to these advanced supportive care measures, even where they are available, remains limited in poor-resource settings. In this context, patient triage is of prime importance. The NEWS2 score appears to be a useful marker of severity that is compatible with operational constraints; however, it omits important risk factor variables that have been included in the PREDS scoring model developed here.

Two previously-published study attempted to generate a scoring system for evaluation of death. Our colleagues in Sierra Leone developed a score including age, level of education, occupation and symptom description.[28] Similarly, Hartley et al proposed a score based on age, symptom at triage and day since first symptom).[29] Nonetheless, none of those scores include biological and virological parameters, and the use of some socio-demographical data are not easily replicable across different field. Finally, the score developed by Kangbai et al is too complicated (5 groups and up to 9 sub groups of variables) to be used during outbreaks. PREDS, on the other hand, does include those biological and clinical data, which might help early distinction of patients requiring immediate advanced supportive care from those at a lower risk of negative outcome. Moreover, in view of the data currently available in case of epidemics, its operational feasibility is high. The NEWS2 has demonstrated its simplicity in large cohorts of Lassa fever patients,[30] standard biological devices are now widely deployed in ETCs and viral load is systematically performed at patient admission. We have also developed a form to be filled in for the calculation of the PREDS score and the determination of the risk level at admission (annex 5). In the framework of our study we propose, with the aim to improve survival rates, that patients who score 6 or more (medium or high PREDS score) should benefit immediately from innovative advanced care. This aggressive strategy should be tested with external cohorts to confirm its general applicability and accuracy.

This study has some limitations. First, due to its observational nature, it did not allow the effects of advanced supportive care to be distinguished from those of specific investigational treatments on mortality rates. Second, PREDS was only internally validated and requires external validation in future epidemics in the field. Third, data collection was a major challenge in the field context (war in the region, extremely isolated sites), leading to issue in data quality and missingness. To address missing data, we conducted a sensitivity analysis using multiple imputed validation datasets to test the external validity of the prediction model and subsequent risk-scoring system, which indicated that the model performed well on these multiple imputed held-out datasets. Finally, our study population was heterogeneous, because some patients were vaccinated and some received specific treatment or benefit from advanced supportive care which might alter the interpretation of case fatality rate. However, it should be underlined that this study was set up in real life condition, and reflects the daily life of field teams.

In conclusion, despite the development of specific treatments for EVD, mortality remains high, especially in patients who present with critical symptoms on admission to the ETC. Improving the availability of advanced supportive care is therefore essential as a first step in strategic management of the disease. In addition, early triage after admission at the ETC, aimed at identifying patients at risk of death, is key to managing strategies. The PREDS score allows this early referral of patients to appropriate medical care for them. Considering the trends in EVD cases in recent outbreaks, it is likely that interventions will be carried out at multiple small ETCs quickly set up near to where cases of the disease develop, and that PREDS will be useful in this regard for identifying severe cases at these small intervention units.

Contributors

Marie Jaspard (MJ), Sabue Mulangu (SM), Sylvain Juchet (SJ), Beatrice Serra (BS), Richard Kojan (RK), Xavier Anglaret (XA) and Denis Malvy (DM) designed the study.

MJ, SM, SJ, BS, RK, Hans-Joerg Lang (HJL), Ibrahim Dicko (ID), Baweye Mayoum Baka (BMB), Gaston Musemakweli Komanda (GMK), Jeremie Muhindo Katsavara (JMK), Jean Louis Muanza Nyengele (JLM),

Patricia Kabuni (PK), Fabrice Mbika Mambu (FMM), Margaux Isnard (MI), Christophe Vanhecke (CV), Alexia Letord (AL), Olivier Tshiani (OT, Fiston Isekusu (FE, Jean Luc Biampata (JB) and Jean Jacques Muyembe (JM) set up the study in DRC, enrolled and monitored the patients and recorded clinical data.
MJ, SM, SJ, BS, Ibrahima Dieye (ID), Oscar Peterrson-Lomba (OPS) had access to the raw data.
MJ, SM, SJ, BS, ID, OPL, Khaled Ezzedine (KE) carried out the analyses. MJ, SM, SJ, BS, RK, Moumouni Kinda (MK), KE and DM drafted the manuscript.
All authors revised the manuscript critically for important intellectual content and approved the final version before submission.

Data sharing statement

The anonymized individual data and data dictionary for the study will be made available to other researchers by Professor Denis Malvy (denis.malvy@chu-bordeaux.fr) after a methodologically sound proposal has been approved and a data access agreement signed.

Declaration of interests

No conflict of interest is declared by any of the authors.

SM is listed as the inventor on the patent application for mAb 114, US Application No.62/087, 087 (PCT Application No.PCT/US2015/060733) related to anti-Ebola virus antibodies and their use.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101699.

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