Development of a case fatality prognostic score for HIV-associated histoplasmosis

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A B S T R A C T

Objectives: The burden of histoplasmosis is as great as that of tuberculosis in Latin America and the attributable mortality is even higher. A better assessment of severity could help reduce mortality.
Methods: From the French Guiana HIV-histoplasmosis database, we attempted to identify factors associated with 30-day death after antifungal drug initiation and constructed a prognostic score. We evaluated its discrimination performance using several resampling methods.
Results: Of the 415 patients included, 56 (13.5%) died within 30 days of treatment. The fatality-associated factors were performance status ≥3, altered mental status, dyspnea, C-reactive protein ≥75 mg/l, hemoglobin <9 g/dl and/or a platelet <100000/ml, and an interstitial lung pattern on chest X-ray. We constructed a 12-point prognostic score. A threshold ≥5 classified patients as alive or dead at 30 days with a sensitivity of 84%, a specificity of 81%, a positive predicted value of 40%, and a negative predicted value of 97%. The area under the curve of the receiver operating characteristic curves from the different resamples were stable between 0.88 and 0.93.
Conclusion: The histoplasmosis case fatality score, which is easy and inexpensive to perform, is a good tool for assessing severity and helping in the choice of induction therapy. An external validation remains necessary to generalize these results.

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Introduction

Histoplasma capsulatum var. capsulatum is suspected to be responsible for up to one-fifth of AIDS-related deaths in Latin America [1]. Progressive HIV-associated histoplasmosis has consistently been the leading opportunistic infection and used to be the leading cause of mortality among patients infected with HIV in French Guiana [2,3] and probably in much of South and Central America. Hence, the burden of HIV-associated histoplasmosis among patients infected with HIV in Latin America is at least as great as that of tuberculosis [1]. In addition to diagnostic difficulties and lack of awareness in most endemic countries, the high mortality resulting from HIV-associated histoplasmosis is explained by the challenge of assessing its severity and starting timely adapted antifungal therapy. American histoplasmosis can affect various organs and evolve subacutely, resulting in a late diagnosis and a possible underestimation of the severity.

Liposomal amphotericin B is the first-choice molecule for the most severe forms [4] but holds drawbacks: the complexity of its preparation and administration, frequent and severe side effects (hypokalemia, acute renal failure), a high cost, and unavailability in many countries, which use the cheaper, more toxic deoxycholate amphotericin B [5,6]. Itraconazole is used as the first-line treat-

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ment in moderate forms [7], but its pharmacokinetics can lead to a delayed therapeutic response [8], and the numerous drug interactions can lead to insufficient concentrations and therapeutic failures [9,10]. These characteristics, associated with its fungistatic effect, presumably explain the longer sterilization time of cultures under itraconazole than under amphotericin B [4,7].

The first World Health Organization guidelines about HIV-associated histoplasmosis among people living with HIV [11] distinguish mild, moderate, moderately-severe, and severe forms, without clear distinction between classes and potential variations from one physician to another. Some authors have already attempted to identify clinical and biological markers associated with mortality [7,12–19], without any quantifiable predictive performance. Given the potential importance of the initial therapeutic choice, it is crucial to reliably recognize which patients are at risk of dying from it.

Hence, we wished to develop a clinical prognostic score of mortality of HIV-associated histoplasmosis that would be usable in low-resource areas to help physicians in their clinical evaluation and therapeutic decisions.

Methods

Study population

We included patients from the previously described French Guiana histoplasmosis retrospective cohort, involving the hospitals of Cayenne, Saint-Laurent-du-Maroni, and Kourou. Clinical, paraclinical, therapeutic, and outcome data were systematically collected by trained research technicians from 1982 to 2020 [20]. Of note, paraclinical data were collected within the week before antifungal initiation. The inclusion criteria were age ≥18 years, confirmed HIV infection (enzyme-linked immunosorbent assay + Western blot), first episode of HIV-associated disseminated histoplasmosis confirmed by direct examination (May-Grunwald-Giemsa or Grocott-Gomori methenamine silver staining, Supplementary Material, picture S1) and/or culture of *Histoplasma capsulatum var. capsulatum*, according to the case definition of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group [21], updated in 2020 [22]. The exclusion criterion was history of histoplasmosis.

Case definition

Early death was defined as death occurring within 30 days (D30) of antifungal therapy initiation. Patients lost to follow-up before D30 were considered alive.

Modelization and prognosis score development

Variables of interest

The explanatory variables were selected from the patients' available clinical, biological, radiographic, and therapeutic data. We did not include "local" variables, such as location, length of stay in French Guiana, or ethnicity, because these variables would not be relevant in other contexts. We considered variables already identified as associated with mortality in the literature, and their association in our cohort. We performed a bivariate analysis (Student's t-test or Wilcoxon test for quantitative variables and χ^2 test or Fisher's exact test for binary and categorical variables). We retained clinically relevant variables with a statistically significant association (P <0.2). Three adjustment variables were always retained in the explanatory model, regardless of their statistical significance: age, T cluster of differentiation 4 (TCD4) lymphocytes

count, and inclusion period (<2000, 2000-2010, 2011-2020). We calculated the Pearson correlation coefficients between the quantitative, binary, and ordinal data to ensure that they were not too correlated with each other (threshold at ± 0.5).

Management of missing data

Variables of interest with a missing data rate (NA for not available) ≥20% were excluded because it was impossible to assert that the character was missing at random. For the remaining variables, we looked for an imbalance in the distribution of NA among dead and alive patients at D30, which would have been in favor of not missing at random data. Second, we performed multiple imputations using the multivariate imputation by chained equations method [23].

Explanatory regression model and discretization of quantitative variables

A first explanatory logistic regression model was carried out with all the retained explanatory variables to assess their independent contribution to the outcome. The binary variables included in the model were coded as present or absent. For continuous variables, linearity was assessed using partial residual plots of the explicative logistic regression model, with mathematical transformation of these variables, if necessary. Discretization of quantitative variables was carried out after multiple imputations to retain as much information as possible. The threshold values were set using several approaches: by supervised discretization according to the minimum description length principle [24], then manually, based on clinically relevant thresholds already existing in the literature and on the variables' partial residual plots. Aggregations of variables were performed when relevant.

Construction of the predictive model

We constructed a predictive model based on the explanatory model with only binary or ordered categorical variables, removing the adjustment variables, and using the Akaike information criterion to obtain the most parsimonious model.

Construction of a clinical score

Once the predictive model was validated, the explanatory variables were weighted by dividing their coefficients by the smallest of them and rounding to the nearest integer.

Score performance

The association between the score and 30-day mortality was examined. The score calibration was evaluated graphically. The discrimination of the score from the predictive model was evaluated using a receiver operating characteristic curve analysis and the calculation of the area under the curve. Because there was no pre-existing equivalent score, we did not perform a reclassification.

Internal validation of the predictive model

To perform an internal validation of the predictive model, we first recalculated it by randomly separating our population into a training sample (3/4) and a testing sample (1/4). Then, we performed the same type of analysis taking the Cayenne and Kourou hospitals as the training sample and patients from Saint-Laurent-du-Maroni as the testing sample. We also used resampling methods: leave-one-out (or Jackknife cross-validation [25]) and bootstrap.632 [26].

Software and packages

Statistics were done using R 4.0.2, with the tidyverse 1.3.0 [27], tableone 0.13.0, mice 3.14.4 [23], discretization 1.0-1.1, forestmodel 0.6.2, ROCR 1.0-1.1 [28], pROC 1.18.0 [29], predtools0.0.2, and caret 6.0-93 packages.

Results

Characteristics of the population

We included the 415 patients of the cohort. Their baseline characteristics according to survival at D30 are presented in Table 1. All 14 patients lost to follow-up before D30 were considered alive. A total (13.5%) of patients died within the first D30 of treatment; the median time to death was 7 days (interquartile range: 2-14 days).

Development of the explanatory model

Among the 21 variables significantly associated with mortality showing a missing data rate <20%, we discarded nine that seemed clinically nondiscriminant: fever was present in 84.8% of the survivor group and 96.4% of the deceased group; the relevance of respiratory symptoms was only explained by dyspnea, whereas cough was more frequent in the survivor group, as was lymphadenopathy; the relevance of neurologic symptoms was explained by alteration of mental status, whereas headache was more frequent in the survivor group; the relevance of abnormal thoracic X-ray was explained by interstitial lung pattern, whereas pulmonary alveolar condensation was more frequent in the survivor group; the difference in the mean neutrophil count between the two groups was not clinically relevant; creatininemia was not included because we did not have data on the previous creatinine level or diuresis, and the large variance did not allow identification of a discriminating threshold. The missing data were imputed before discretization for the following variables: World Health Organization Performance status (5 NA, 1.2%), dyspnea (2 NA, 0.5%), altered mental status (2 NA, 0.5%), interstitial lung pattern on the X-ray (75 NA, 18,1%), TCD4 lymphocyte count (8 NA, 2%), hemoglobinemia (15 NA, 3.6%), platelet count (16 NA, 3.9%), aspartate aminotransferase (ASAT) concentration (18 NA, 4.3%), C-reactive protein (CRP) concentration (43 NA, 10.4%), and lactate dehydrogenase concentration (57 NA, 13.7%). The results of the explanatory model are presented in Table 2. Performance status ≥3 (odds ratio [OR] = 5.33, 95% confidence interval [CI] = 2.03-15.43), altered mental status (OR = 9.67, 95% CI = 2.97-33.79), and dyspnea (OR = 3.96, 95% CI = 1.44-11.20) were significantly associated with death at D30. CRP concentration ≥75 mg/l (OR = 5.42, 95% CI = 2.30-13.73) and the presence of both anemia <9 g/l and thrombocytopenia <100,000/ml (OR = 4.92, 95% CI = 1.53-16.81) were also significantly associated with death at D30. The presence of only one of these cytopenia also seemed to be associated with mortality (OR = 2.05, 95% CI = 0.78-5.81), as did the presence of an interstitial lung pattern on chest X-ray (OR = 2.08, 95% CI = 0.79-5.46). Because the inclusion period was significantly associated with survival as an adjustment variable, we looked for a significant interaction between this variable and the other explanatory variables. None were identified.

Development of the clinical prognostic score

After removing the adjustment variables, the most parsimonious predictive model and score were obtained (Table 3). The histoplasmosis case fatality score (HFS), calculated with seven criteria (patient's performance status ≥3, alteration of mental status, dyspnea, interstitial lung pattern on the chest X-ray, CRP level >75 mg/dl, anemia <9 g/dl, and/or platelet count <100,000/ml, ranged from 0 [no prognostic marker] to 12 [all markers]. The median score of our population was 3 (interquartile range: 1-5; minimum: 0; maximum: 12).

Validation of the histoplasmosis case fatality score

The graphical evaluation of the HFS calibration, presented in Figure 1, showed a properly calibrated score: the higher the score, the greater the proportion of early deaths. The evaluation of the discrimination of the prognostic model by the receiver operating characteristic curve obtained from the source population, as well as by the train/test, leave-one-out, and bootstrap.632 methods, are presented in Figure 2. The area under the curve remained stable between the methods (between 0.88 and 0.94), supporting a nonoverfitted model.

Selection of the HFS threshold

For a discrimination threshold of ≥5 (Supplementary Figures 1 and 2), we obtained an accuracy of 81% (95% CI = 77-85), a sensitivity of 84% (95% CI = 73-93), a specificity of 81% (95% CI = 76-84), a positive predictive value of 40% (95% CI = 33-49), and a negative predictive value of 97% (95% CI = 95-99). For a discrimination threshold of ≥7, we obtained an accuracy of 92% (95% CI = 89-94), a sensitivity of 63% (95% CI = 50-75), a specificity of 96% (95% CI = 94-98), a positive predictive value of 73% (95% CI = 58-86), and a negative predictive value of 94% (95% CI = 92-96). Considering the high mortality rate of HIV-associated histoplasmosis, identifying all patients requiring intensive treatment is essential, thus the greater sensitivity displayed by the threshold of five seemed preferable. Nine patients with an HFS <5 died; their characteristics are summarized in Table S1 (Supplementary Material). All had fever, five had a performance status ≥3, the remaining had a performance status of 2. None had dyspnea or altered mental status. Four had anemia <9 g/dl, two had platelet count <100,000/ml, and four had CRP <75 mg/l. Eight had a chest X-ray, and three had interstitial lung pattern. Three of them were initially treated with liposomal amphotericin B.

Of the 298 patients with no missing data for all HFS criteria before imputation, 66 had a score ≥5, of whom 21 (32%) had not received amphotericin B (deoxycholate or liposomal) induction treatment. Their median score was 7 (interquartile range: 5-7; maximum: 10).

Discussion

Here, we showed, in the largest published cohort of patients with HIV-associated histoplasmosis, that the 12-point HFS assessment before treatment initiation appears to reliably identify patients at risk of death within D30 of treatment. This simple inexpensive score requires only clinical examination, blood count, CRP measurement, and chest X-ray. These characteristics are essential because this disease mostly impacts regions with limited resources. An HFS <5 seemed to properly identify patients at low risk of mortality. It could determine which patients can be managed in a conventional care unit and treated initially with itraconazole, avoiding toxic and costly amphotericin B. Patients with a score ≥5—the threshold with the greatest sensitivity—should benefit from close monitoring and be treated with amphotericin B, preferably liposomal [11], especially because the median time to death was 1 week in our cohort, which approximately corresponds to the time needed to reach effective blood concentrations of itraconazole [8]. Although the score seemed to perform well in training and in testing samples, it still requires external validation before it can be used in routine care. A score calculator is already available on the internet (http://cicec-antilles-guyane.org/hfs), facilitating its use and helping the realization of other validation studies.

Although the retrospective nature of this hospital cohort and some missing data may lead to limitations, this is the largest pub-

Table 1

Baseline characteristics according to survival at 30 days of antifungal initiation among the population of historical HIV-associated histo-plasmosis cases, 1982-2020, French Guiana.

Characteristic	Alive at day 30	Dead at day 30	p-value	NA (%)
n (%)	359 (86.5)	56 (13.5)		0 (0.0)
Hospital (%)			0.495	0 (0.0)
Cayenne	240 (66.9)	38 (67.9)		
Kourou	36 (10.0)	3 (5.4)		
Saint-Laurent-du-Maroni	83 (23.1)	15 (26.8)		
Inclusion period (%)			**<0.001**	**0 (0.0)**
1982-1999	69 (19.2)	29 (51.8)		
2000-2010	170 (47.4)	18 (32.1)		
2011-2020	120 (33.4)	9 (16.1)		
Mean age (SD)	40.7 (9.9)	39.7 (10.1)	0.491	0 (0.0)
Male gender (%)	233 (64.9)	36 (64.3)	1.000	0 (0.0)
History of opportunistic infection (%)	85 (23.7)	13 (23.2)	1.000	0 (0.0)
Other concomitant opportunistic infection (%)	159 (44.3)	26 (46.4)	0.877	0 (0.0)
Diagnosis of HIV infection concomitant with the episode (%)	285 (79.4)	42 (75.0)	0.568	0 (0.0)
WHO Performance Status (%)			**<0.001**	**5 (1.2)**
0	10 (2.8)	0 (0.0)		
1	40 (11.3)	0 (0.0)		
2	174 (49.2)	8 (14.3)		
3	105 (29.7)	34 (60.7)		
4	25 (7.1)	14 (25.0)		
Weight loss (%)	159 (44.3)	39 (69.6)	0.868	198 (47.7)
Mean systolic blood pressure in mmHg (SD)	105.6 (18.5)	103.0 (19.9)	0.523	175 (42.2)
Fever (%)	301 (84.8)	54 (96.4)	**0.032**	**4 (1.0)**
Median duration of fever in days (IQR)	21 [10-30]	30 [15-30]	0.228	171 (41.2)
Mean maximum temperature in°C (SD)	39.29 (0.85)	38.96 (1.37)	**0.120**	200 (48.2)
Respiratory symptoms (%)	174 (48.7)	40 (71.4)	**0.003**	**2 (0.5)**
Thoracic pain (%)	11 (3.1)	0 (0.0)	0.376	
Dyspnea (%)	39 (10.9)	33 (58.9)	**<0.001**	
Cough (%)	152 (42.6)	18 (32.1)	**0.184**	
Sputum (%)	39 (10.9)	4 (7.1)	0.531	
Hemoptisis (%)	5 (1.4)	2 (3.6)	0.540	
Cutaneous signs (%)	42 (11.8)	10 (17.9)	0.289	2 (0.5)
Mucosal signs (%)	42 (11.8)	5 (8.9)	0.596	2 (0.5)
Superficial lymphadenopathy (%)	191 (53.5)	21 (37.5)	**0.037**	2 (0.5)
Digestive signs (%)	255 (71.4)	36 (64.3)	0.351	2 (0.5)
Neurologic signs (%)	67 (18.8)	19 (33.9)	**0.015**	**2 (0.5)**
Altered mental status (%)	14 (3.9)	16 (28.6)	**<0.001**	
Meningeal syndrome (%)	8 (2.2)	2 (3.6)	0.893	
Cerebellar syndrome (%)	2 (0.6)	0 (0.0)	1.000	
Focal deficit (%)	7 (2.0)	3 (5.4)	0.285	
Epileptic seizures (%)	1 (0.3)	0 (0.0)	1.000	
Peripheral neuropathy (%)	6 (1.7)	1 (1.8)	1.000	
Headache (%)	29 (8.1)	0 (0.0)	**0.054**	
Acute adrenal failure (%)	2 (0.6)	0 (0.0)	1.000	2 (0.5)
Abnormal chest X-ray (%)	121 (42.2)	38 (71.7)	**<0.001**	**75 (18.1)**
Interstitial lung pattern (%)	92 (32.1)	36 (67.9)	**<0.001**	
Alveolar condensation (%)	15 (5.2)	5 (9.4)	0.380	
Pleural effusion (%)	7 (2.4)	4 (7.5)	**0.131**	
Nodules (%)	13 (4.5)	4 (7.5)	0.560	
Thoracic lymphadenopathy (%)	8 (2.8)	2 (3.8)	1.000	
Abnormal thoracic computed tomography-scan (%)	114 (79.2)	13 (92.9)	0.379	257 (62.0)
Interstitial lung pattern (%)	30 (21.0)	9 (64.3)	**0.001**	
Micronodules (%)	55 (38.5)	9 (64.3)	**0.111**	
Median T CD4 lymphocyte count/μl (IQR)	35 [13-77]	20 [7-48]	**0.002**	**8 (2.0)**
Range of T CD4 lymphocyte count/μl	0-590	0-98		
Median T CD8 lymphocyte count/μl (IQR)	284 [152-524]	175 [99-394]	0.345	194 (46.7)
Median HIV viral load in log10 (IQR)	5.3 [4.7-5.7]	5.4 [5.1-5.8]	0.238	279 (67.2)
Mean hemoglobinemia in g/dl (SD)	9.28 (2.04)	8.18 (1.88)	**<0.001**	**15 (3.6)**
Median neutrophils count/ml (IQR)	1800 [810-2935]	2118 [1344-3864]	**0.057**	**17 (4.1)**
Median platelets count in g/l (IQR)	198 [111-274]	93 [40-178]	**<0.001**	**16 (3.9)**
Median creatininemia in μmol/l (IQR)	76 [63-95]	88 [77-127]	**0.008**	**10 (2.4)**
Mean albuminemia (SD)	24.83 (6.84)	18.82 (7.64)	**0.001**	265 (63.9)
Median ASAT concentration in UI/l (IQR)	54 [33-90]	73 [33-145]	**0.010**	**18 (4.3)**
Median ALAT concentration in UI/l (IQR)	29 [19-50]	29 [19-52]	0.806	19 (4.6)
Median GGT concentration in UI/l (IQR)	92 [52-202]	94 [55-230]	0.805	47 (11.3)
Median ALP concentration in UI/l (IQR)	146 [82-281]	185 [99-349]	0.204	48 (11.6)
Median C-reactive protein concentration in mg/l (IQR)	46 [17-88]	119 [78-148]	**<0.001**	**43 (10.4)**
Median lactate dehydrogenase concentration in UI/l (IQR)	393 [277-740]	834 [377-1840]	**<0.001**	**57 (13.7)**
Median ferritinemia in μg/l (IQR)	1208 [546-3059]	3884 [1725-14097]	**0.025**	204 (49.2)
Median triglyceridemia in g/l (IQR)	1.7 [1.2-2.24]	1.7 [1.5-2.6]	0.523	265 (63.9)
Mean prothrombin ratio (SD)	78.99 (16.46)	66.17 (23.33)	**0.001**	171 (41.2)
Mean fibrinogen concentration in g/l (SD)	3.15 (1.45)	2.58 (1.30)	0.203	329 (79.3)
Induction treatment with liposomal amphotericin B (%)	123 (34.3)	17 (30.4)	0.316	11 (0.03)

SD, standard deviation; NA, not available; IQR, interquartile range; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phenyl phosphatase.

According to their distribution, continuous variables are presented as mean (SD) or median (IQR).

Among bold *P*-values corresponding to *P* <0.2, bold NA-values corresponding to NA<0.2.

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Table 2

Explanatory model of death within 30 days of initiation of antifungal therapy in patients presenting HIV-associated histoplasmosis

Variable		N	Odds ratio	p
Inclusion time period	1982-1999	98	Reference	
	2000-2010	188	0.24 (0.08, 0.68)	0.009
	2011-2020	129	0.26 (0.06, 1.05)	0.068
Age ≥ 40	No	205	Reference	
	Yes	210	1.14 (0.51, 2.57)	0.746
CD4 < 50/µL	No	273	Reference	
	Yes	142	0.90 (0.33, 2.37)	0.841
Performance status ≥ 3	No	235	Reference	
	Yes	180	4.77 (1.85, 13.49)	0.002
Altered mental status	No	385	Reference	
	Yes	30	9.84 (3.02, 34.33)	<0.001
Dyspnea	No	343	Reference	
	Yes	72	3.55 (1.32, 9.77)	0.013
Interstitial lung pattern on the chest X-ray	No	279	Reference	
	Yes	136	2.06 (0.78, 5.38)	0.139
CRP ≥ 75 mg/L	No	264	Reference	
	Yes	151	5.55 (2.37, 14.00)	<0.001
Cytopenia*	No cytopenia	173	Reference	
	One cytopenia	180	2.05 (0.78, 5.78)	0.156
	Two cytopenia	62	4.44 (1.40, 14.87)	0.013
LDH ≥ 2N	No	240	Reference	
	Yes	175	1.18 (0.48, 2.90)	0.715
Induction treatment with liposomal amphotericin B	No	269	Reference	
	Yes	146	0.78 (0.26, 2.36)	0.652

0.1 0.2 0.5 1 2 5 10 20

Adjusted odds ratio from logistic regression coefficients with 95% confidence interval
*One Cytopenia (anaemia <9g/dL **or** thrombocytopenia <100000/ml) and two cytopenia (anaemia <9g/dL **and** thrombocytopenia <100000/ml)
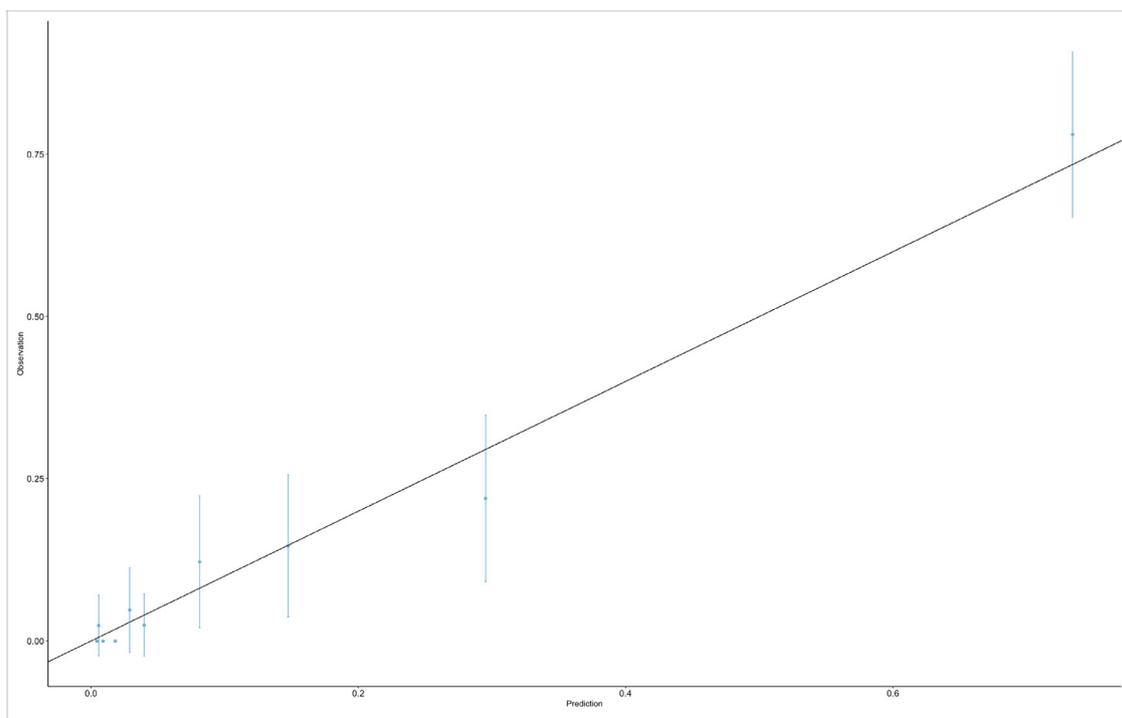
Figure 1. Graphical evaluation of the histoplasmosis case fatality score calibration.

Table 3
Predictive model of death within 30 days of initiation of antifungal therapy in patients presenting HIV-associated histoplasmosis and prognosis score scale construction (HFS)

Variable		N	Odds ratio		p	HFS
Performance status ≥ 3	No	235		Reference		
	Yes	180		5.60 (2.35, 14.87)	<0.001	+2
Altered mental status	No	385		Reference		
	Yes	30		6.62 (2.18, 21.23)	0.001	+3
Dyspnea	No	343		Reference		
	Yes	72		3.87 (1.54, 9.94)	0.004	+2
Interstitial lung pattern on the chest X-ray	No	279		Reference		
	Yes	136		2.09 (0.84, 5.16)	0.107	+1
CRP ≥ 75 mg/L	No	264		Reference		
	Yes	151		5.45 (2.44, 13.06)	<0.001	+2
Cytopenia*	No cytopenia	173		Reference		
	One cytopenia	180		2.35 (0.93, 6.39)	0.080	+1
	Two cytopenia	62		5.74 (2.00, 17.64)	0.001	+2

Adjusted odds ratio from logistic regression coefficients with 95% confidence interval
HFS : Histoplasmosis case-Fatality Score, obtained by dividing the model's explanatory variable coefficients by the smallest of them and rounding to the nearest integer
*One cytopenia (anaemia <9g/dL or thrombocytopenia <100000/mL) and two cytopenia (anaemia <9g/dL and thrombocytopenia <100000/mL)
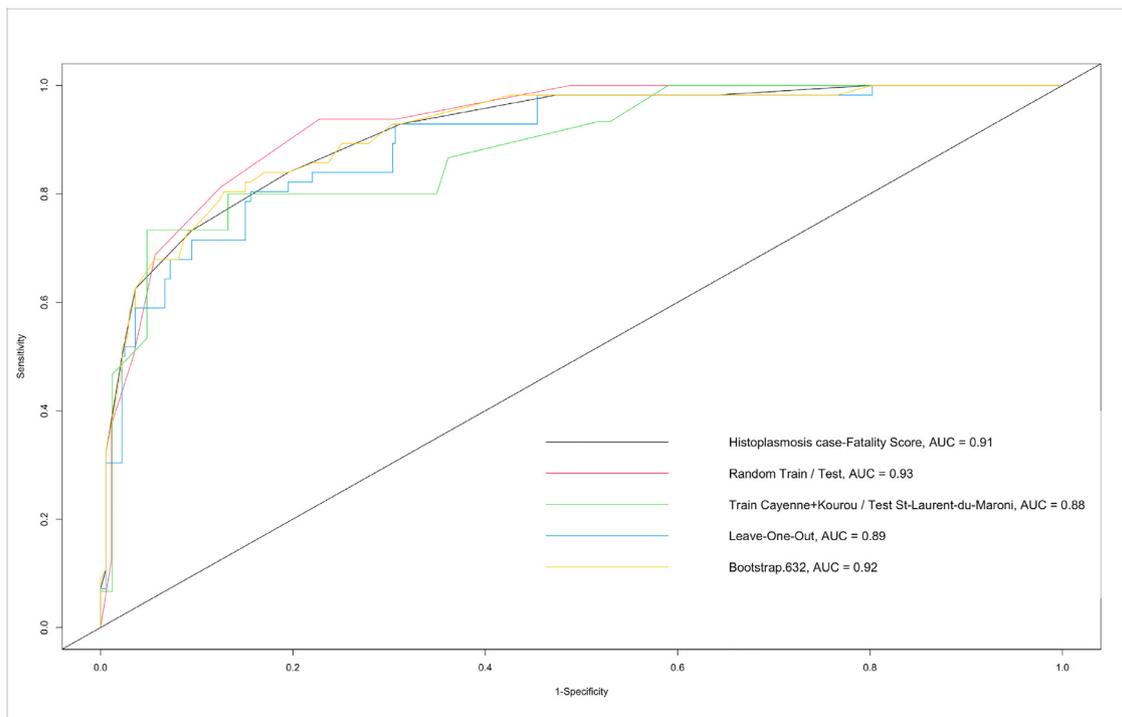
Figure 2. Receiver operating characteristic curves of the histoplasmosis case fatality score and cross-validations models.
AUC, area under the curve.

- Histoplasmosis case-Fatality Score, AUC = 0.91
- Random Train / Test, AUC = 0.93
- Train Cayenne+Kourou / Test St-Laurent-du-Maroni, AUC = 0.88
- Leave-One-Out, AUC = 0.89
- Bootstrap.632, AUC = 0.92

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lished cohort worldwide. Even though several studies have identified variables associated with death or intensive care management, no simple and discriminating scoring system to quantify the risk of death is available to date. As in our series, profound impairment of general condition, dyspnea, and thrombocytopenia have been reported associated with mortality [7,14,16,30]. Some criteria identified in these studies have not been surveyed or were quite rare in our cohort. Moreover, they already are criteria for intensive care management (hemodynamic or respiratory failure) or markers of hemophagocytic lymphohistiocytosis (ASAT elevation, hyperferritinemia, hypertriglyceridemia) [31,32], which also requires aggressive management. Hypoalbuminemia was deeper in the deceased group, but the difference was not clinically relevant (18.82 g/l and 24.83 g/l). Furthermore, biological inflammatory syndrome, represented in our model by an elevated CRP concentration, was an independent marker of mortality and was probably a confounding factor because it favors hypoalbuminemia [33]. Although it was significantly associated with survival status and had minimal missing data, creatinine concentration was not retained in our model because the baseline values for each patient and diuresis were not available. Acute renal failure could, however, be an independent marker of mortality because it complicates therapeutic management and has been identified as such in previous studies. Chest X-ray was preferred over computed tomography (CT) scan for several reasons in addition to the high rate of missing data for CT scan, mostly in cases that occurred in earlier decades. Chest X-ray is a simple and inexpensive examination, it is widely available, it does not require an experienced radiologist for interpretation, and although a CT scan can be more sensitive by detecting abnormalities that are not visible on X-ray, an interstitial lung pattern visible on X-ray is probably more specific for severe forms.

We chose the date of antifungal treatment initiation as the reference date rather than the date of diagnosis because histoplasmosis diagnosis was rarely established at the time of treatment initiation in our cohort and was sometimes only confirmed *postmortem*. Indeed, clinical examination, laboratory, and imaging findings may suggest the diagnosis but are not specific and can hardly rule out other infections, like tuberculosis [34]. Moreover, co-infection is not uncommon in these populations [35].

As can be seen in our series, assessment of the severity of HIV-associated histoplasmosis is difficult. Based on the HFS results, 21 (32%) of the 66 patients with no missing data and a HFS ≥ 5 should have benefited from amphotericin B. Among the nine patients who died despite an HFS<5, eight had a score of ≥ 3, mostly due to a performance status ≥ 3 and biological abnormalities. Ferritinemia occured in four of them and was above 2000 µg/l in three of them. These three patients presented with hepatomegaly and ASAT >2N. Two presented with splenomegaly and anemia <9 g/l. Two had triglycerides titration; their levels were 1.42 g/l for one and 5.4 g/l for the other. The H-scores [31] of these three patients ranged from 57% to 97%, in favor of a hemophagocytic lymphohistiocytosis due to HIV-associated histoplasmosis [32] without clinical signs of organ failure upon treatment initiation. Because hemophagocytic lymphohistiocytosis already requires aggressive treatment of the cause, the HFS brings nothing for patients diagnosed with this syndrome because they are known to be severe. The five other patients died on an average of 6 days after the initiation of itraconazole. This induction treatment must be associated with close clinical and biological monitoring during the first week. It would be relevant to reassess the HFS after 5-7 days of antifungal therapy.

The 13.5% mortality rate in our cohort from French Guiana is probably lower than in resource-limited regions. Indeed, the French Guianese population benefits from an acute care management system similar to that of mainland France and improvement in medical care, earlier antiretroviral treatment, and increased awareness of histoplasmosis over the past decades, independent of

specific antifungal treatment, have probably reduced the mortality in this population, as shown in the explanatory model and suggested in an earlier study [36]. However, the inclusion period did not significantly interact with the HFS variables, which allowed us to ignore it for the predictive model calibration. We believe that excluding health care system context-related variables from the score makes it adequate for both well-developed and low-resource countries.

Conclusion

At present, antifungal treatment choice relies on severity, which is somewhat subjective. Using a simple score as a proxy of case severity definition at the patient's bedside is less prone to interpretation and helps optimize antifungal treatment choice. The HFS is a simple, inexpensive, calibrated, and discriminating score. An HFS <5 is associated with a negative predictive value of 97% (95% CI = 95-99), and therefore, a risk of death at D30 $\leq 5\%$ suggests choosing itraconazole treatment. By contrast, patients with an HFS ≥ 5—associated with a risk of death D30 >33%—should receive some amphotericin B formulation, preferably the liposomal form. After external validation, the HFS may become a valuable tool for the therapeutic decision making of clinicians facing HIV-associated histoplasmosis, including resource-limited endemic areas.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

The database has received approval by the Comité Consultatif pour le Traitement de l'Information pour la Recherche en Santé (CCTIRS) (no. 10.175bis, 6 October 2010), the French National Institute of Health and Medical Research Institutional Review Board (CEEI INSERM) (IRB0000388, FWA00005831 18 May 2010), and the Commission Nationale Informatique et Libertés (no. JZU0061856X, 16 July 2010).

Author contributions

UF searched the literature, created the figures and tables, and wrote the first draft. MN and AA designed and oversaw the project and performed the analysis. UF, MN, and AA performed the formal data analysis. MN, MBW, LE, CT, MD, JFC, FD, PC, and AA reviewed and edited the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.03.048.

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