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Development and validation of a score for the diagnosis of reactive hemophagocytic syndrome (HScore)

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Accepted Article

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Accepted Article

Abstract

Background: Because there are no specific clinical, biological or histological features, reactive hemophagocytic syndrome may be difficult to distinguish from other diseases such as severe sepsis or hematological malignancies. The aim of this study was to develop and validate a diagnostic score for reactive hemophagocytic syndrome.

Methods: A multicenter retrospective cohort of 312 patients with a positive (n=162), negative (n=104) or undetermined (n=46) diagnosis of reactive hemophagocytic syndrome was used to construct and validate the score. Ten explanatory variables were evaluated for their association with the diagnosis of hemophagocytic syndrome and logistic regression was used to calculate the weight of each criterion included in the score. Performances of the score were defined using developmental and validation datasets.

Results: Nine clinical (i.e., known underlying immunodepression, maximal temperature, organomegaly), biological (i.e., triglyceride, ferritin, SGOT, and fibrinogen levels, cytopenia), and cytological (i.e., hemophagocytosis features on bone marrow aspirates) variables were retained in the HScore. Score points assigned to each variable ranged from 0 to 18 for a known underlying immunodepression up to 0 to 64 for triglycerides level. The median [IQ range] HScore was 230 [203-257] for patients with a positive diagnosis of reactive hemophagocytic syndrome and 125 [91-150] for patients with a negative diagnosis. The probability of having hemophagocytic syndrome ranged from less than 1% for a HScore lower than 90 to more than 99% for a HScore greater than 250.

Conclusion: HScore can be used to estimate an individual's risk of having reactive hemophagocytic syndrome. This score is freely available online (http://saintantoine.aphp.fr/score/).

Accepted Article

Hemophagocytic syndrome is a hyperinflammatory condition caused by highly stimulated but unregulated and often ineffective immune response. The cardinal features are fever, hepatosplenomegaly, pancytopenia, and widespread histiocytic tissue infiltration. There are two major forms of hemophagocytic syndrome, a primary (hereditary) form which occurs during the first years of life, and a secondary (reactive) form which occurs at any age and which is probably much more frequent than the primary form (1–5). The reactive hemophagocytic syndrome may be related to infections, malignancies or autoimmune diseases (6–10), mainly in a context of underlying immunodepression. The reactive hemophagocytic syndrome is a severe, life-threatening condition with a fatal outcome ranging from 10% in children with systemic juvenile idiopathic arthritis to 20-60% in adults with malignancy-associated hemophagocytic syndrome (4,11). A timely diagnosis is essential since early administration of an efficient therapy (e.g., etoposide) may improve survival (12). However, the diagnosis of hemophagocytic syndrome is difficult since there are no specific clinical, biological or pathological features. Bone marrow hemophagocytosis may be observed in the absence of proven hemophagocytic syndrome, in particular after blood transfusion or in critically ill septic patients (13–15). The clinical (e.g., fever, hepatosplenomegaly) and biological (e.g., cytopenia, hyperferritinemia) features observed in patients with hemophagocytic syndrome are also non specific and the syndrome may be difficult to distinguish from other diseases such as severe sepsis or hematological malignancies. Diagnostic criteria sets have been proposed (1,8,16–19) but they suffer from substantial limitations. First, some have been proposed in pediatric populations or to diagnose the primary form of hemophagocytic syndrome, mostly observed in a context of hereditary disease. They have never been validated in adults nor in the reactive form of the syndrome. Second, the weight of each criterion included in these scores is unknown and the proposed cut-off values were empirically defined. Third, some of the proposed criteria (e.g. NK cell

Accepted Article

activity, soluble interleukin-2-receptor level) are unavailable in routine practice and may be of low interest for the diagnosis of the reactive form of the syndrome. In this context, the aim of this study was to construct and validate a set of weighted diagnostic criteria for the diagnosis of reactive hemophagocytic syndrome.

Material and methods

Patients

Between June and November 2012, we retrospectively reviewed all the forms for and all the results of bone marrow aspirations performed between January 2006 and December 2011 in three French tertiary university hospitals. First, all forms asking for bone marrow aspiration for a suspected hemophagocytic syndrome and all bone marrow aspirations which concluded to hemophagocytosis were identified. Second, we identified all patients coded in these centers during the study period as D76.1 (hemophagocytic lymphohistiocytosis), D76.2 (hemophagocytic syndrome, infection-associated) or D76.3 (other histiocytosis syndromes) according to the International Classification of Diseases (ICD-10). The two resulting lists of patients were crossed in order to make sure that no patient with a code for hemophagocytic syndrome who has had bone marrow aspirate was missed. We then retrospectively reviewed the medical files of all the corresponding patients. Medical information was extracted via a standardized questionnaire, including demographic (age, gender), clinical (highest recorded temperature, duration of fever (if any), presence of hepato-, spleno- or adenomegaly, past medical history, known underlying immunodepression (i.e., people suffering from HIV or chronically treated with an immunosuppressive therapy such as glucocorticoids, cyclosporine, or azathioprine), diagnosis of hemophagocytic syndrome retained or not by the medical team in charge of the patient, treatment prescribed, underlying disease, transfer in intensive care unit, outcome), biologic (leucocytes and platelets counts, hemoglobin, liver enzymes, ferritin,

Accepted Article

triglycerides, cholesterol, fibrinogen, C-reactive protein, lactate dehydrogenase (LDH), blood urea nitrogen, creatinine and sodium levels, prothrombin time) and pathologic (hemophagocytosis on bone marrow aspirations or biopsies) items. The biological parameters extracted from the medical records were those available on the day of bone marrow aspiration, or those available up to two days before or after in the absence of data on the simultaneous day. Only the first episode was considered in patients with recurrent hemophagocytic syndrome.

Classification procedure

In a first step, three of us (LF, LG, PC) classified cases into 3 groups: hemophagocytic syndrome likely (positive cases), hemophagocytic syndrome possible (undetermined cases), hemophagocytic syndrome unlikely (negative cases). Classification was based on information extracted from the patient's medical record., Those who classified the patients had follow-up data and information about the underlying disease. Each investigator classified patients blindly of the others' classification and of the results of the Delphi study conducted at the same time and described elsewhere (20). Once the three investigators had classified all the patients, the results were compared. Positive/undetermined and undetermined/negative classifications were considered as minor discordances whereas positive/negative classifications were considered as major discordances. All cases of minor discordances were discussed between the three investigators and conciliation towards a consensus was obtained in many cases. In cases where a consensus was not reached or initial classification led to major discordances, a fourth expert (OL) was involved and a final classification was obtained when three of the four experts were in agreement, the remaining cases being classified as undetermined cases. Each of the four experts involved in this classification procedure had at

Accepted Article

least ten years of experience in diagnosing and caring of patients with reactive hemophagocytic syndrome.

Variables of interest

Ten explanatory variables were evaluated for their association with the diagnosis of hemophagocytic syndrome. These 10 variables were those issued from a Delphi consensus study described elsewhere (20). In summary, 63 international experts in reactive hemophagocytic syndrome were solicited between October and December 2012 and 24 experts originating from 13 countries participated in the second and final Delphi round. The questionnaire explored their opinion regarding the helpfulness of a predefined list of criteria for the positive diagnosis of reactive hemophagocytic syndrome. This Delphi survey showed that a positive consensus (i.e., criteria considered by the experts as "absolutely required" or "important") was reached for the seven following criteria: uni-, bi- or pancytopenia, presence of hemophagocytosis pictures on bone marrow aspirate or biopsy, fever, organomegaly, presence of a predisposing underlying disease, and high levels of LDH or ferritin. A negative consensus was reached for 13 criteria. No consensus was reached for 4 criteria (i.e., high transaminases and triglyceride levels, and low fibrinogen and glycosylated ferritin levels). We included in the present study all the seven criteria cited above plus three out the four criteria for which no consensus was reached. We chose not to include the percentage of glycosylated ferritin as this parameter is very rarely assessed in clinical practice.

Statistical analysis

To develop the diagnostic score, undetermined cases were excluded. Considering the positive and negative cases, 90% were randomly assigned to the developmental data set, while the remaining 10% were assigned to the validation data set. Positive and negative cases were

Accepted Article

compared using the Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. Univariate analyses evidenced that each of the 10 variables of interest were associated with the positive diagnosis of reactive hemophagocytic syndrome with a p-value <0.05. They were therefore included in a multivariate logistic model to assess their independent contribution to the outcome. Binary variables (e.g., hemophagocytosis features on bone marrow aspirate) included in the model were coded as present or absent. For continuous variables, linearity was checked using the log-likelihood ratio test. In order to define a score easy to use, variables showing a linear relationship with the outcome were dichotomized. The threshold value was based on a receiver operating characteristic (ROC) curve analysis, retaining the value that maximized (sensitivity + specificity). For variables not showing a linear relationship to the outcome, the LOWESS (locally weighted least squares) smoothing function was used to suggest ranges for each variable, the resulting plot being examined to identify cut-off values. No interaction terms were included in the model. The pseudo-R^2 statistic was used for assessing the goodness-of-fit of the model. The resulting coefficients of this multiple logistic regression analysis were used to assign score points for construction of HScore. For each variable significantly associated to the outcome in the logistic regression, the rule was to multiply the beta for each range by 10 and round off to the nearest integer. Once the score was calculated for each case from the developmental data set, it was used in another multiple logistic regression equation designed to be converted to a probability of suffering from hemophagocytic syndrome. An equation based on this multiple logistic regression model was developed. The first step was to compute the logit as follows: logit=beta0 + beta1(HScore) after verifying that the HScore was normally distributed. The second step was to convert this logit to a probability of hemophagocytic syndrome with the following equation $Pr(y=1/logit)=e^{logit}/(1+e^{logit})$. Lastly, to assess the performance of the system, Hosmer-Lemeshow tests were performed on both the developmental and validation

Accepted Article

sets to evaluate calibration (21) and areas under ROC curves were used to evaluate discrimination. Continuous variables are presented as median and 25th to 75th percentile values. Categorical variables are presented as proportions. Missing data were left as missing. All analyses were performed using Stata, version 11.1 (StataCorp, College Station, Tex.). Construction of HScore shares many methodological features with the study by Le Gall et col describing the construction and validation of the SAPSII score (22).

Results

Study population

Of the 314 patients identified, 2 were excluded because of insufficient available data to be classified. Considering the remaining 312 patients, 196 (63%) were male and their median age was 51 [36-64] years (Table 1). Regarding their classification, initial perfect consensus, initial minor discordances and initial major discordances involved 179 (57%), 96 (31%, with 78 cases conciliated after discussion) and 37 (12%) patients, respectively. The fourth expert opinion was therefore required for 55 (18%) cases. At the end of the process, an agreement (i.e., same classification for at least 3 experts) was reached for 304 out of 312 patients, the 8 remaining patients being therefore classified as undetermined. The variables of interest for the 162 (52%) patients classified as positive, the 104 (33%) patients classified as negative, and the 46 (15%) patients classified as undetermined are reported in Table 2. The most frequently missing data were ferritin and triglyceride levels which were missing for 14% and 9% of patients, respectively.

Construction of HScore

Accepted Article

The developmental data set included 238 patients, amongst whom 29 were not taken into account in the multivariate analysis because at least one data was missing. All patients but two included in this study had at least one cytopenia and we were therefore unable to assess the risk of having hemophagocytic syndrome when no cytopenia was present. ROC curve analyses resulted in defining each cytopenia as hemoglobin level ≤ 9.2 g/dl, leucocytes count ≤ 5000/mm^3 or platelets count ≤ 110 000/mm^3. Two cytopenias was defined as any combination of two cytopenias and three cytopenias as all cytopenias combined. In multivariate analysis, 9 out of the 10 variables included in the model were still significantly associated with the probability of being classified as positive hemophagocytic syndrome (Table 2). LDH level was not independently associated with the positive diagnosis of hemophagocytic syndrome (*p*-value = 0.72 for level between 500 and 2000 UI/L and *p*-value=0.19 for level > 2000 UI/L as compared to the reference level < 500 UI/L). The pseudo-R^2 statistic for the model was 0.78 ($p<0.0001$). Score points assigned to each variable varied from 0 to 18 for an underlying immunodepression up to 0 to 64 for triglycerides level (Table 4). Missing data were scored 0. The median HScore was 230 [203-257] for positive cases and 125 [91-150] for negative cases. The probabilities of having hemophagocytic syndrome according to HScore values are reported in Table 5. The best cut-off value for HScore was 169, corresponding to a sensitivity of 93%, a specificity of 86% and a good classification of 90% of the patients.

Performances of HScore

In the validation set, the median HScore was 222 [202-284] for positive cases and 129 [77-152] for negative cases. The goodness-of-fit test performed on the developmental data set show a *p*-value of 0.93. When the HScore was applied to the validation data set, the *p*-value was 0.76, suggesting that the model can be accurately applied in other patients than those in

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whom the model was developed. The areas under ROC curve for the HScore were 0.97 and 0.95 in the developmental and validation data sets, respectively, indicating excellent discrimination (Figure 1).

HScore in undetermined cases

The median HScore was 169 [142-189] in the set of the 46 undetermined cases. Of those 46 patients, 11 (24%) had a HScore corresponding to a probability greater than 80% to have hemophagocytic syndrome and 12 (26%) had a HScore with a corresponding probability lower than 20%.

Discussion

HScore is the first validated score devoted to the diagnosis of reactive hemophagocytic syndrome. Score construction was based on the largest dataset of adult patients with suspected reactive hemophagocytic syndrome reported to date. This score is made on nine clinical, biological, and cytological variables, appropriately weighted.

Hemophagocytic syndrome is a complex disease which may affect a number of different organs, so signs and symptoms may be extremely variable (2,4,23) and no finding is pathognomonic of the disease. In this context, different sets of criteria have been proposed for helping clinicians to diagnose the syndrome (1,8,16–19). However, as described above, these criteria sets suffer from major limitations. Since hemophagocytic syndrome may be difficult to distinguish from severe sepsis or flare-up of the underlying disease (e.g., systemic lupus erythematosus, Still disease, lymphoma) (9,24–26) the availability of a simple score predicting the individual probability of suffering from the syndrome constitutes a major advance, allowing clinicians to make adequate therapeutic decision at the earliest opportunity.

Accepted Article

So far, hemophagocytic syndrome is considered as a rare condition. However, it is probably under diagnosed due to the lack of defined diagnostic criteria. For clinicians not used with the diagnosis, hemophagocytosis features on bone marrow aspirate or any other tissue biopsy is often considered as the gold standard for the diagnosis. However, there is no consensus amongst cytologists regarding which cytological features are necessary and sufficient for the diagnosis and, in the published literature, the cytological criteria used to define hemophagocytosis are rarely reported (13–15,19). Moreover, hemophagocytosis features are commonly found in severely ill people, out of the context of hemophagocytic syndrome (13–15). For instance, Francois et al reported hemophagocytosis in 32 out of 50 (64%) patients presenting with a sepsis syndrome and thrombocytopenia <100000 G/L (13). In another study, hemophagocytosis was evidenced in bone marrow of 69 (65%) out of 107 patients who died in a medical intensive care unit (14). Conversely, initial bone marrow examination of patients suffering from authentic hemophagocytic syndrome may only show erythroid hyperplasia, leading inexperienced clinicians to wrongly reject the diagnosis. This is reported in almost half of cases of hemophagocytic syndrome (27). Cytological features of hemophagocytosis should therefore not be considered as the gold standard for the diagnosis of hemophagocytic syndrome.

Variables included in the multivariate analysis were those issued from the Delphi study involving a panel of experts in the reactive for of hemophagocytic syndrome (20). Among these variables, LDH level was considered as absolutely required or important by 75% of the experts but was not independently associated with the diagnosis of reactive hemophagocytic syndrome according to our analyses. On the other hand, other variables such as low fibrinogen or high triglyceride levels were considered as absolutely required or important by "only" 52 to 62% of the experts in the Delphi study but were strongly associated with the

Accepted Article

positive diagnosis of hemophagocytic syndrome in our study, confirming that some of the criteria for which no consensus was reached finally revealed useful.

The proposed HScore has several strengths. First, it is the first available set of criteria developed with an adequate methodology. The selection of variables and the weights assigned to levels of these variables were based on the combined use of a Delphi survey and a logistic regression modeling. This differs from the previous sets of criteria that were solely based on clinical judgment. Even though the variables statistically associated with the diagnosis of hemophagocytic syndrome were those usually recognized by others as helpful diagnostic criteria (18,23), the design of our study enabled to estimate the appropriate threshold values for each variable and to assess the appropriate weight of each one in the diagnosis of hemophagocytic syndrome. Second, our large study population was made of patients suffering from reactive hemophagocytic syndrome of different etiologies. The good performance of HScore on both the developmental and the validation data set ensures that the model is correctly calibrated to the range of diseases associated with hemophagocytic syndrome. Lastly, data collection required to calculate the HScore is very simple and quick. This ease of use, coupled with the fact that the HScore is freely available online (http://saintantoine.aphp.fr/score/) should result in its widespread acceptance and its use in daily practice.

HScore has some limitations as well. First, it is based on a retrospective study population with the possibility of bias in selection of this population. To minimize this bias and to ensure that no patient fulfilling our inclusion criteria was missed, we selected the study population by reviewing both the forms and results of bone marrow aspirations and the ICD-10 classification of patients. We thus verified that the few patients coded a hemophagocytic syndrome who did not have bone marrow aspiration were mostly patients with a recurrence of hemophagocytic syndrome who therefore could not be included in our analyses. A bias in

Accepted Article

data recording may also be hypothesized. However, the medical files of patients were reviewed by investigators familiar with the syndrome, using a standardized procedure. Moreover, because of the severity of the syndrome, only few data were missing at time of bone marrow aspiration. The second main limitation relates to the classification of patients. This classification was considered as the gold-standard and was therefore central in the construction of the HScore. In order to ensure that the cases and the controls were adequately classified four investigators with a good expertise regarding hemophagocytic syndrome analyzed all the files independently and blindly of each other and of the results of the Delphi study run at the same time. Since there is no pathognomonic finding in hemophagocytic syndrome and thus no gold standard for the diagnosis, we believe that the global procedure that was used enabled to classify the patients as correctly as possible. Patients for whom no consensus was reached were classified as undetermined and were therefore not included in the analyses aimed at HScore construction and validation. Unsurprisingly, these patients' HScore large distribution reflects the large spectrum of this "difficult to diagnose" group of patients. Therefore, although it is impossible to evaluate the performance of the HScore in this population, this score might be considered the best available tool to date for guiding diagnosis decision in all patients. Another limitation is related to the fact that the diagnostic approach to hemophagocytic syndrome may partly depend on the underlying disease, each disease being associated with particular biological abnormalities (e.g., elevated white blood cell counts and serum ferritin in patients with Still's disease, cytopenias in patients with lupus erythematosus). Therefore, the cut-off values for biological criteria may depend of the underlying disease and, ideally, these cut-offs should have been assessed separately for each of them. However, this is made difficult by the rarity of this entity. Lastly, we chose to favor the development of the score rather than its validation in this initial study. Therefore, we decided to include in the validation dataset only 10% (n=27) of the overall population.

Accepted Article

Although the score performances found in this validation population make us confident about the robustness of HScore, the low number of patients used to cross-validate the score combined with the retrospective design of the study make prospective validation of the score in other samples of patients needed before recommending its widespread use.

In conclusion, the present work made possible the construction of a diagnostic score which aim is to help clinicians in diagnosing the syndrome in daily practice. The score is freely available online in order to facilitate its use. Further research should evaluate the HScore robustness on other series of patients and should assess the performances of the HScore in the diagnosis of the primary form of hemophagocytic syndrome.

Accepted Article

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Accepted Article

Accepted Article

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Accepted Article

Table 1: characteristics of the study population

	negative patients N= 104 (33%)	undetermined patients N= 46 (15%)	positive patients N=162 (52%)	P*
Male	57 (55%)	30 (65%)	109 (67%)	0.03
Age (years)	54 [39-65]	55 [37-68]	48 [35-62]	0.02
Underlying disease				
hematological malignancy**	28 (27%)	14 (31%)	92 (57%)	
infection***	35 (34%)	25 (54%)	40 (25%)	
hematological malignancy + infection	1 (1%)	0 (0%)	6 (4%)	
systemic lupus erythematosus	6 (6%)	2 (4%)	3 (2%)	
Still's disease	1 (1%)	1 (2%)	2 (1%)	
solid cancer	5 (5%)	0 (0%)	5 (3%)	
other/unknown	28 (26%)	4 (9%)	14 (8%)	
Diagnosis of HS retained by the medical team who took care of the patient	19 (19%)	29 (63%)	148 (92%)	<0.0001

* for the comparaison between positive and negative patients

** mainly Hodgkin (n=27) and non Hodgkin (n=84) lymphoma

*** mainly bacteria (n=51) and mycobacteria (n=22)

Accepted Article

Table 2: variables of interest according to classification of patients

	negative patients N= 104 (33%)	undetermined patients N= 46 (15%)	positive patients N=162 (52%)	p*
Known immunodepression**	34 (33%)	12 (26%)	73 (45%)	0.03
Maximal temperature (°C)	38.6 [37.9-39.2]	39.2 [38.3-39.8]	39.5 [39.0-40.2]	<0.0001
Hepato- or splenomegaly	23 (22%)	12 (26%)	28 (17%)	<0.0001
Hepato- and splenomegaly	31 (30%)	15 (33%)	105 (65%)	
Hemophagocytosis features on bone marrow aspirate	41 (39%)	36 (78%)	114 (70%)	<0.0001
Leucocytes count (10^6/L)	4900 [2160-10400]	5780 [2200-9000]	3100 [1800-6500]	0.004
neutrophiles	3100 [1260-6400]	4625 [1600-7910]	2150 [1080-4160]	0.02
lymphocytes	800 [480-1300]	690 [350-1400]	610 [300-1150]	0.05
monocytes	310 [150-740]	360 [160-840]	230 [90-440]	0.02
Hemoglobin (g/dL)	9.6 [8.4-10.4]	9.0 [8.4-9.6]	8.3 [7.3-9.2]	<0.0001
Platelets (10^9/L)	82 [44-196]	54 [29-102]	59 [30-92]	<0.0001
Ferritin (ng/mL)	755 [254-1935]	2079 [1350-4000]	5139 [2612-10 000]	<0.0001
Triglycerides (mmol/L)	1.89 [1.17-2.70]	2.72 [1.78-4.35]	3.06 [2.16-4.18]	<0.0001
Fibrinogen (g/L)	4.3 [3.3-6.3]	4.4 [3.0-5.9]	3.8 [2.1-5.4]	0.004
LDH (UI/L)	642 [420-933]	660 [377-1053]	908 [513-1865]	0.0005
SGOT (UI/L)	44 [26-84]	63 [27-141]	69 [31-171]	0.0004
SGPT (UI/L)	31 [17-64]	36 [16-110]	38 [21-89]	0.14

* for the comparaison between positive and negative patients

** HIV or chronic immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine…)

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Table 3: variables included in the development of HScore

	Coef	Standard error	p
Known underlying immunodepression	1.81	0.86	0.03
Temperature (°C)			
<38.4	1	-	
38.4-39.4	3.35	1.09	0.002
≥39.5	4.89	1.30	<0.0001
Organomegaly			
no	1	-	
hepatomegaly or splenomegaly	2.33	1.03	0.02
hepatomegaly and splenomegaly	3.80	1.16	0.001
Cytopenia *			
cytopenia of one lineage	1	-	
cytopenia of two lineages	2.41	1.00	0.02
cytopenia of three lineages	3.36	1.15	0.003
Ferritin (ng/mL)			
<2000	1	-	
2000-6000	3.46	0.94	<0.0001
>6000	5.01	1.28	<0.0001
Triglyceride (mmol/L)			
<1.5	1	-	
1.5-4	4.45	1.44	0.002
>4	6.40	1.74	<0.0001
Fibrinogen (g/L)			
>2.5	1	-	
≤ 2.5	2.96	1.42	0.04
SGOT (UI/L)			
<30	1	-	
≥30	1.86	0.98	0.06
Hemophagocytosis features on bone marrow aspirate	3.49	1.01	<0.0001

* defined as hemoglobin level ≤ 9.2 g/dl and/or leucocytes count ≤ 5000/mm^3 and/or platelets count ≤ 110 000/mm^3

Table 4: HScore

	0 point	18 points	19 points	23 points	24 points	30 points	33 points	34 points	35 points	38 points	44 points	49 points	50 points	64 points
Known underlying immunodepression	no	yes												
Temperature (°C)	<38.4						38.4-39.4					>39.4		
Organomegaly	no			HM or SM						HM & SM				
Number of cytopenia*	1				2			3						
Ferritin (ng/mL)	<2000								2000-6000				>6000	
Triglyceride (mmol/L)	<1.5										1.5-4			>4
Fibrinogen (g/L)	>2.5					≤ 2.5								
SGOT (UI/L)	<30		≥ 30											
Hemophagocytosis features on bone marrow aspirate	no								yes					

* defined as hemoglobin level ≤ 9.2 g/dl and/or leucocytes count ≤ 5000/mm^3 and/or platelets count ≤ 110 000/mm^3

HM : hepatomegaly; SM: splenomegaly

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Table 5: probability of hemophagocytic syndrome according to HScore

HScore	Probability of hemophagocytic syndrome
90	<1%
100	1%
110	3%
120	5%
130	9%
140	16%
150	25%
160	40%
170	54%
180	70%
190	80%
200	88%
210	93%
220	96%
230	98%
240	99%
250	>99%

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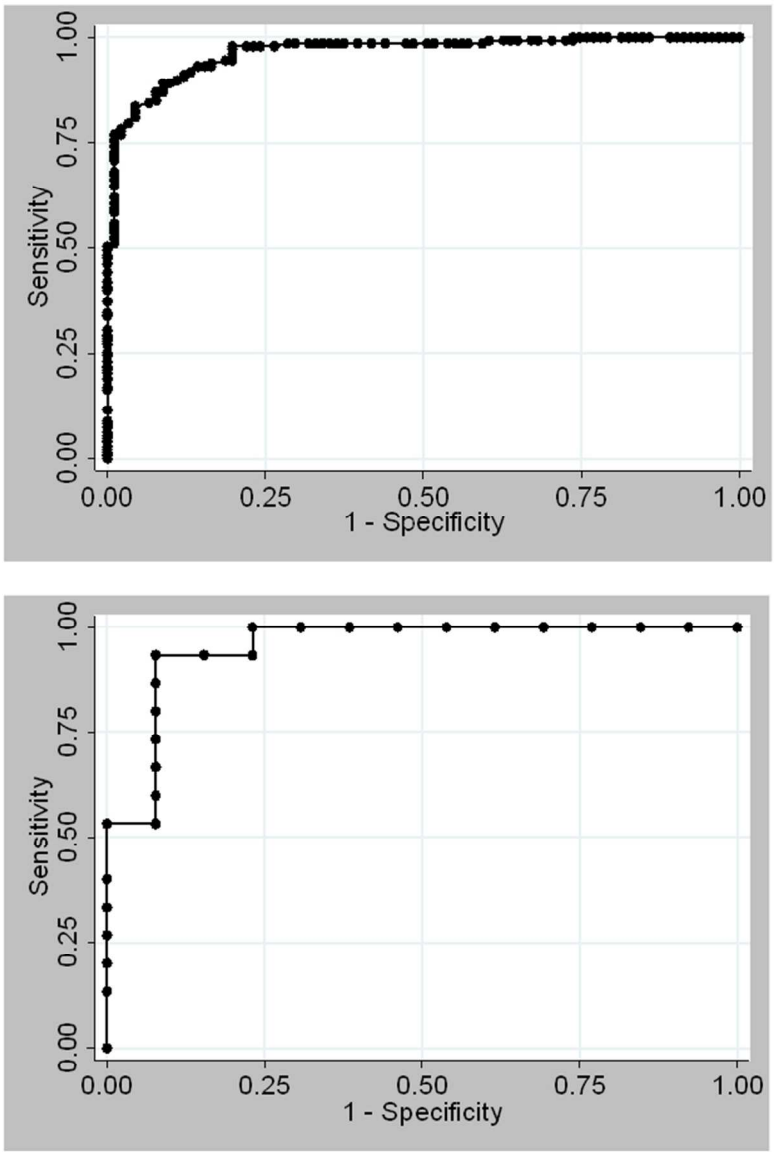
Figure legend:

Figure 1: Area under ROC curve for the HScore in the developmental (top) and validation (bottom) data sets



Area under ROC curve for the HScore in the developmental (top) and validation (bottom) data sets
190x254mm (96 x 96 DPI)