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TITLE PAGE

Clinical research study

Reactive hemophagocytic syndrome in adults: A multicenter retrospective analysis of 162 patients

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L. Fardet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
L. Fardet and S. Rivière did the statistical analyses, interpreted the data and wrote the manuscript.
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ABSTRACT

Objectives: Current knowledge in reactive hemophagocytic syndrome mainly relies on single-centre case series including a relatively small number of patients. We aimed to identify a multicenter large cohort of adult patients with reactive hemophagocytic syndrome and to describe relevant clinical and laboratory features, underlying conditions and outcome.

Methods: We conducted a multicenter study in three tertiary care centres in France over a 6-year period. The medical files of 312 patients with suspected hemophagocytic syndrome were retrospectively reviewed. Patients were classified with a positive, negative or undetermined diagnosis of hemophagocytic syndrome by experts' consensus.

Results: Among the 312 patients fulfilling our inclusion criteria, 162 patients were classified as positive hemophagocytic syndrome (male: 67%, median age: 48 [35-62] years). Compared to patients without hemophagocytic syndrome, they suffered more frequently from an underlying immunodepression (45% versus 33%, p=0.03) and they exhibited higher temperature, ferritin, triglycerides, AST, biririubin, LDH and CRP and lower haemoglobin, leucocytes, platelets and sodium levels. Noteworthy only 70% of them had hemophagocytosis features on bone marrow aspiration. Haematological malignancies, especially non-Hodgkin lymphomas, were the main trigger of hemophagocytic syndrome, accounting for 56% of cases. The early mortality rate (i.e. within one month after diagnosis) was 20%. Patients with haematological malignancies-associated hemophagocytic syndrome had a poorer early outcome than those with underlying infection.

Conclusion: In this large, multicentre study, haematological malignancies are the main disease associated with hemophagocytic syndrome in adults. Early mortality is high and outcome is influenced by the underlying disease.

Key words: hemophagocytic syndrome, hemophagocytic lymphohistiocytosis, adult, lymphoma, infection, outcome

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INTRODUCTION

Hemophagocytic syndrome is a rare but life-threatening disease, caused by an uncontrolled immune response, resulting in a hyperinflammatory disease. Main clinical and biological features are prolonged high fever, hepatosplenomegaly and cytopenias with histiocytic infiltration in bone marrow and other tissues. It was first described in 1939 by Scott and Robb-Smith as "histiocytic medullary reticulosis".[1] In 1952, a familial disorder termed familial hemophagocytic reticulosis was reported and in the following decades,[2] hemophagocytic syndromes related to various disorders such as infections and rheumatic diseases were described .[3-5] Nowadays the classification of hemophagocytic syndrome by the Histiocyte Society distinguishes the primary (genetic) and secondary (reactive) form.[6] In the primary form, which comprises familial hemophagocytic syndrome and hemophagocytic syndrome associated with several inherited immune deficiencies,[7] symptoms usually occur in the first years of life. The secondary (i.e., reactive) form can occur at any age and is much more frequent than the primary form.[8] It can be triggered by various underlying conditions, mainly infections, malignancies or autoimmune diseases.[9-12]

Diagnosis of reactive hemophagocytic syndrome is challenging. Clinical and biological features are non specific and can be encountered in severe sepsis or haematological malignancies. On the other hand, hemophagocytosis patterns have been described in critically ill patients or after transfusion or cytotoxic therapies, out of a context of hemophagocytic syndrome.[13]

Since current knowledge in reactive hemophagocytic syndrome mainly relies on single-centre case series including a relatively small number of patients, we conducted a retrospective, multicenter study over a 6-year period in order to identify all adult patients with suspected reactive hemophagocytic syndrome. From this large cohort of patients we described relevant clinical and laboratory features, underlying conditions and outcome.

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. All forms requesting bone marrow aspiration for a suspicion of hemophagocytic syndrome and all bone marrow aspirations which concluded to hemophagocytosis were identified. Besides we identified all patients coded in these centres during the study period as D76.1 (hemophagocytic lymphohistiocytosis), D76.2 (hemophagocytic syndrome, infection-associated) or D76.3 (other histiocytosis syndromes) following the International Classification of Diseases (ICD-10). The two resulting lists of patients were crossed in order to ensure that no patient with a code for hemophagocytic syndrome who underwent a bone marrow aspirate was missed. We then retrospectively reviewed the medical records of all the corresponding patients and medical information was extracted via a standardized questionnaire. The following clinical conditions were evaluated: age, gender, highest recorded temperature, duration of fever (if any), presence of hepato-, spleno- or adenomegaly, past medical history and diseases known at the time of suspicion of hemophagocytic syndrome, known underlying immunodepression (i.e., people known to suffer from Human Immunodeficiency Virus (HIV) or to be chronically treated with an immunosuppressive therapy such as glucocorticoids, cyclosporine, or azathioprine), treatment prescribed, underlying disease, transfer in intensive care unit and outcome. Laboratory data such as leucocytes and platelets counts, hemoglobin, liver enzymes, ferritin, triglycerides, cholesterol, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH), blood urea nitrogen, creatinine and sodium levels, and prothrombin time were collected on the day of the bone marrow aspiration or in the two preceding or following days. The presence or absence of hemophagocytosis on bone marrow aspiration was recorded. Finally, the diagnosis

retained by the medical team in charge of the patient was recorded. For patients with recurrent hemophagocytic syndrome, only the first episode was considered.

Classification procedure

In a first step, three investigators involved in the diagnosis and treatment of adult patients with hemophagocytic syndrome (LF, LG, and PC) classified patients into 3 groups: hemophagocytic syndrome likely (positive cases), hemophagocytic syndrome possible (undetermined cases), and hemophagocytic syndrome unlikely (negative cases). Classification was based both on information available at time of hemophagocytic syndrome diagnosis and on follow-up data regarding the hemophagocytic syndrome or the underlying disease. Each investigator classified patients blindly of the others' classification. 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. 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.

Statistical analysis

Continuous variables are presented as median and 25^{th} to 75^{th} percentile values. Categorical variables are presented as proportions and their 95% confidence intervals indicating precision of estimates. Cases classified as positive were compared to those classified as negative using the Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. For the analyses, missing data were left as missing, no multiple imputations were performed.

In patients with a positive diagnosis of hemophagocytic syndrome, the short term (i.e., within one month after bone marrow aspiration) survival was assessed using a Kaplan-Meier method. This short term survival was compared between haematological malignancies-associated and infection-associated hemophagocytic syndrome using the Log-Rank test.

RESULTS

Diagnosis of hemophagocytic syndrome

A total of 314 patients fulfilled the inclusion criteria. Two were excluded because of insufficient available data to be classified. Considering the remaining 312 patients, initial perfect consensus, initial minor discordances and initial major discordances concerned 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 of 312 patients, the 8 remaining patients being classified as undetermined. Diagnosis of hemophagocytic syndrome was likely (positive cases) for 162 (52%) patients and unlikely (negative cases) for 104 (33%) cases. Undetermined cases represented 15% of the study population (n = 46). This classification procedure is summarized in Figure 1.

Clinical and laboratory features

Clinical, biological and pathological characteristics of the 3 groups are reported in Table 1. The most frequently missing data were ferritin and triglyceride levels which were missing for 14% and 9% of patients, respectively. Analyses compared the positive and negative groups. Fever, organomegaly, lymphadenopathy were clinical hallmarks present in each group but at a higher degree in the positive group. Organ failure leading to ICU admission was also more frequent in the positive group. Among laboratory features, cytopenias, prothrombin time and

fibrinogen on the one side and triglycerides and ferritin on the other were significantly lower and higher in the positive group, respectively. We further observed significant differences in other biological parameters. Aspartate aminotransferase (AST), LDH and CRP were higher whereas serum sodium level was lower in the positive group. Interestingly, hemophagocytosis was found in bone marrow aspiration in only 70.4% of patients with a positive diagnosis of hemophagocytic syndrome and in 39.4% of patients for whom the diagnosis was finally rejected. Sensitivity and specificity of bone marrow aspiration for diagnosis of hemophagocytic syndrome was thus 70.4% and 60.6%, respectively.

Underlying diseases

Details on the underlying conditions in each group are given in Table 2. Among the 162 patients with a positive diagnosis of hemophagocytic syndrome, hematological malignancies (in particular non-Hodgkin lymphomas) were the most frequent underlying disease, affecting 92 (56.8%) patients. Infections were considered as trigger of hemophagocytic syndrome in 40 (24.4%) patients. Concomitant haematological malignancy and active infection were found in 6 (3.7%) patients. Noteworthy, 73 (45.1%) patients were immunodepressed (i.e., HIV or immunosuppressive therapy) at time of hemophagocytic syndrome (Table 1).

Outcome

Among the 162 positive patients, 61 (37.7%) did not receive any specific treatment for the hemophagocytic syndrome, most of them being only treated for the underlying disease. Among the 101 patients being prescribed a specific treatment, 58 (57.4%) received only glucocorticoids (n=19) or etoposide (n=39), 42 (41.6%) received both glucocorticoids and etoposide and one suffering from infection-associated HS received only intravenous immunoglobulins. Overall, 68 (42%) patients with positive diagnosis of hemophagocytic

syndrome died during follow-up, with 33 (20%) deaths within one month after bone marrow aspiration (Table 1). The one-month survival analysis (Figure 2) demonstrated that patients with haematological malignancies-associated hemophagocytic syndrome have a poorer outcome than those with underlying infection (Log-rank test, p = 0.057).

DISCUSSION

We present here the clinical, biological, cytological and survival data observed in a large and multicenter cohort of adult patients with reactive hemophagocytic syndrome. This work identified several clinical and laboratory features that were strongly associated with the diagnosis of reactive hemophagocytic syndrome. Many of them were consistent with data previously reported (e.g., high fever, cytopenia, hyperferritinemia or coagulopathy). On the other hand, we also identify clinical or biological features that were more surprisingly associated (e.g., sodium, AST or CRP levels, monocytes count) or not associated (e.g., duration of fever, ALT level) with the diagnosis. Other important findings were the absence of hemophagocytosis features in bone marrow aspirate in many patients with hemophagocytic syndrome and the poorer outcome of patients with haematological malignancies-associated hemophagocytic syndrome.

Nearly 30% of the patients with hemophagocytic syndrome did not exhibit any hemophagocytic features on their bone marrow aspirate. On the other hand, more than one third of patients without hemophagocytic syndrome had hemophagocytosis on bone marrow aspirate. Even though these results may seem puzzling, it should be underlined that hemophagocytosis pictures lack specificity and sensitivity for the diagnosis of hemophagocytic syndrome. For instance, hemophagocytosis features are commonly found in severely ill people, out of the context of hemophagocytic syndrome.[14-16] Conversely, initial bone marrow examination of patients suffering from authentic hemophagocytic syndrome

may only show erythroid hyperplasia, without specific features of hemophagocytosis. In pediatric settings, Gupta *et al* described a sensitivity of 60% for hemophagocytosis in initial bone marrow aspirate in patients diagnosed with hemophagocytic syndrome.[17] It is important for the clinicians to be aware that cytological features of hemophagocytosis should not be considered as the gold standard for the diagnosis of hemophagocytic syndrome in order not to rule out the diagnosis in the absence of cytopathologic evidence of hemophagocytosis, which may delay the adequate therapy.

In our study, haematological malignancies, especially non-Hodgkin lymphomas, were by far the main conditions associated with the hemophagocytic syndrome, in higher proportion than in most previous, usually monocenter, case series.[18-21] Among infection-triggered hemophagocytic syndrome, herpes viruses were much less frequent than in Asian countries,[19,21] or in pediatric settings. Noteworthy, nearly half of patients had a known immunodepression at time of hemophagocytic syndrome, mainly related to HIV infection. Interestingly, all the identified causes of immunodepression led to defects in cellular immunity as described in the primary forms, where defects in CD8 T cells and NK cytotoxicity are pivotal.[7] As our patients did not have genetic evaluations, we cannot exclude hypomorphic mutations in the genes involved in the primary forms which could lead to late onset of hemophagocytic syndrome identified as “reactive”.[22]

Mortality rate was high, especially in the first month following the diagnosis. Moreover patients with haematological malignancies had a poorer short-term survival than patients with infection-associated hemophagocytic syndrome. In their study conducted in Japan, Ishii *et al* also described a marked poorer outcome for patients with hemophagocytic syndrome associated with lymphomas compared to those associated with infections or auto-immune diseases.[21] However, they analysed the five-year survival and mortality at this time is more likely to reflect the outcome of lymphomas rather than this of the hemophagocytic syndrome.

In order to try to overcome this issue, we chose to analyse the very early mortality which is more likely to capture the mortality due to the severity of the hemophagocytic syndrome rather than this related to the underlying disease or to the treatment complications. However, in many cases, we acknowledge it was impossible to precisely identify the cause of patients' deaths, several causes being often combined.

This work has several strengths, including the large number of patients, suffering from a large spectrum of trigger diseases and followed in three centers during a six-year period. It has some limitations as well. First, the retrospective design may have resulted in data recording bias. However data were extracted from medical records using a standardized procedure and by physicians experienced in management of hemophagocytic syndrome. Furthermore only few data were missing regarding the variable of interest in this context of severely ill patients. The retrospective design of our study may also have resulted in a bias in selecting the study population. To minimize this risk of 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 could therefore not be included in the analyses. Second, the method used to classify patients may be discussed. Reactive hemophagocytic syndrome is a complex disease with no pathognomonic finding. In this context, different sets of criteria have been proposed for helping clinicians to diagnose the syndrome, including the HLH-2004 diagnostic guidelines.[6,12,19,23-25] However, most of these criteria sets have been defined to diagnose the primary form of the syndrome, mostly observed in a context of hereditary disease. They have never been validated in adults nor in the reactive form. Moreover, some of the proposed criteria (e.g. NK cell 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. Lastly, the weight of each criterion included in these scores is unknown and the proposed cut-off values have been empirically defined. In this context, we chose not to use “pre-defined” criteria to classify the patients. Instead, we preferred to base the classification on an expert consensus. Four investigators with a good expertise in reactive hemophagocytic syndrome analyzed the patients files independently and blindly of each other. For each patient, they had access to the medical, biological and cytological data available at time of hemophagocytic syndrome diagnosis as well as follow-up data including underlying disease, treatment response or occurrence of subsequent episodes of hemophagocytosis. We believe that this was the best way to classify patients as accurately as possible. Using this method it is likely that the patients with the most typical presentations were accurately classified as “positive” and that the patients who were clearly not suffering from hemophagocytic syndrome were classified as “negative”, therefore limiting the risk of classification biases. Moreover, in order to take into account the “grey area” reflecting the overlap between the features of HS and severe infections, malignancies or systemic diseases, we chose to define a third group of patients, i.e., “the undetermined cases”. Some of these patients may have suffered from reactive hemophagocytic syndrome, some others may have not, but, at the end, four experts were unable to agree on the classification of these patients. We believe that these “difficult to classify” patients reflect the daily practice. We also believe that these patients cannot be considered as a group with homogeneous characteristics. For these reasons, we chose to compare the characteristics of the positive group to those of the negative group. By doing this, we evidenced features that were or were not associated with the positive diagnosis of reactive hemophagocytic syndrome, thus helping physicians in diagnose the syndrome in daily practice.

Advances in understanding the pathophysiology of primary hemophagocytic syndrome in the past years have led to revised diagnosis criteria by the Histiocyte Society.[6] However, as

detailed above, such criteria have not been validated in adult populations with the reactive form of the syndrome. By identifying a large multicentre cohort of patients with reactive hemophagocytic syndrome and a control group of patients for whom the diagnosis was finally rejected, we were able to evidence features differentiating these two groups of patients. Further analyses led to the development of a diagnosis score for reactive hemophagocytic syndrome, aiming to help physicians in daily practice.[26]

Competing interests: None

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Table 1. Clinical and laboratory data of the 312 patients.

	Negative patients N= 104 (33.3%)	Undetermined patients N= 46 (14.7%)	Positive patients N=162 (52.0%)	P*
Male	57 (54.8%)	30 (65.2%)	109 (67.3%)	0.03
Age (years)	54 [39-65]	55 [37-68]	48 [35-62]	0.02
Known immunodepression[1]	34 (32.7%)	12 (26.1%)	73 (45.1%)[2]	0.03
Transfer to ICU	39 (37.5%)	30 (65.2%)	88 (54.3%)	0.008
Maximal temperature (°C)	38.6 [37.9-39.2]	39.2 [38.3-39.8]	39.5 [39.0-40.2]	<0.0001
Duration of fever (days)	14 [6-30]	16 [7-30]	15 [10-35]	0.25
Hepato- or splenomegaly	23 (22.1%)	12 (26.1%)	28 (17.3%)	<0.0001
Hepato- and splenomegaly	31 (29.8%)	15 (32.6%)	105 (64.8%)	<0.0001
Lymphadenopathy	25 (24%)	10 (21.7%)	89 (54.9%)	<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
C-reactive protein (mg/L)	72 [15-155]	80 [45-171]	135 [76-205]	<0.0001
Serum sodium (mmol/L)	136 [134-138]	137 [132-140]	133 [129-137]	<0.0001
LDH (UI/L)	642 [420-933]	660 [377-1053]	908 [513-1865]	0.0005
AST (UI/L)	44 [26-84]	63 [27-141]	69 [31-171]	0.0004
ALT (UI/L)	31 [17-64]	36 [16-110]	38 [21-89]	0.14
Total bilirubin (µmol/L)	15 [9-37]	26 [13-54]	24 [12-54]	0.005
GGT (UI/L)	88 [29-211]	106 [45-191]	103 [47-187]	0.27
AP (UI/L)	122 [78-250]	137 [76-184]	135 [86-239]	0.45
Urea (mmol/L)	6.1 [3.4-11.3]	8.3 [4.2-13.0]	7.5 [4.9-12.5]	0.04
Creatinin (µmol/L)	76 [53-133]	85 [57-151]	82 [59-118]	0.57
Prothrombin time (%)	76 [60-90]	72 [55-80]	70 [58-80]	0.02
Fibrinogen (g/L)	4.3 [3.3-6.3]	4.4 [3.0-5.9]	3.8 [2.1-5.4]	0.004
Haemophagocytosis features on bone marrow aspirate	41 (39.4%)	36 (78.3%)	114 (70.4%)	<0.0001
Diagnosis of HS retained by the medical team in charge of the patient	19 (18.6%)	29 (63.0%)	148 (91.9%)	<0.0001

Follow-up (months)	5.4 [0.79-18.5]	3.3 [0.2-14.1]	4.3 [1.1-13.3]	0.15
Overall mortality	37 (35.6%)	21 (45.6%)	68 (42%)	0.31
Death within one month after bone marrow aspiration	23 (22.0%)	16 (34.8%)	33 (20.4%)	0.69

ICU: Intensive are unit; LDH: Lactate dehydrogenase; ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: Gamma glutamyl transferase; AP, alkaline phosphatise; HS: Hemophagocytic syndrome

* For the comparison between positive and negative patients

[1] HIV or chronic immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine…)

2 HIV (n=61), treatment with corticosteroids (n = 8), calcineurin inhibitors (n = 4), azathioprine (n = 1) and infliximab (n=1)

Table 2. Associated diseases in the 3 groups

	Negative patients N= 104 (33.3%)	Undetermined patients N= 46 (14.7%)	Positive patients N=162 (52.0%)
Haematological malignancies	**28 (26.9%)**	**14 (30.4%)**	**92 (56.8%)**
Hodgkin Lymphoma	6 (5.8%)	4 (8.7%)	17 (10.5%)
Non-Hodgkin Lymphoma	17 (17.3%)	10 (21.7%)	57 (35.2%)
T-cell lymphoma	7 (%)	2 (2.2%)	22 (13.6%)
B-cell lymphoma	10 (10.6%)	8 (15.2%)	35 (21.6%)
Castleman disease	2 (1.9%)	0	17 (10.5%)
Other hematological malignancies	3 (2.8%)	0	1 (0.6%)
Infections	**35 (33.6%)**	**25 (54.3%)**	**40 (24.7%)**
Bacteria	24 (23.1%)	18 (39%)	9 (5.5%)
Mycobacteria	5 (4.8%)	4 (8.7%)	13 (8%)
Mycobacterium tuberculosis	4 (8.7%)	4 (8.7%)	12 (7.4%)
Atypical mybobacteria	1(0.6%)	0	1 (0.6%)
Virus	5 (4.8%)	1 (2.2%)	10 (6.1%)
CMV	3 (2.8%)	0	6 (3.7%)
EBV	1 (1%)	0	2 (1.2%)
Other	1 (1%)	1	2 (1.2%)
Parasites [1]	0	1 (2.2%)	6 (3.7%)
Fungi [2]	1 (1%)	1 (2.2%)	2 (1.2%)
Haematological malignancies and infection	**1 (1.0%)**	**0**	**6 (3.7%)**
Systemic disease	**12 (11.5%)**	**3 (2%)**	**5 (3.1%)**
SLE	6 (5.8%)	2 (4.3%)	3 (1.8%)
Still's disease	1 (1%)	1 (2.2%)	2 (1.2%)
Other	5 (4.8%)[3]	0	0
Solid cancer	**5 (4.8%)**	**0**	**5 (3.1%)**
Other / unknown underlying disease	**23 (22.1%)**	**4 (8.7%)**	**14 (8.6%)**

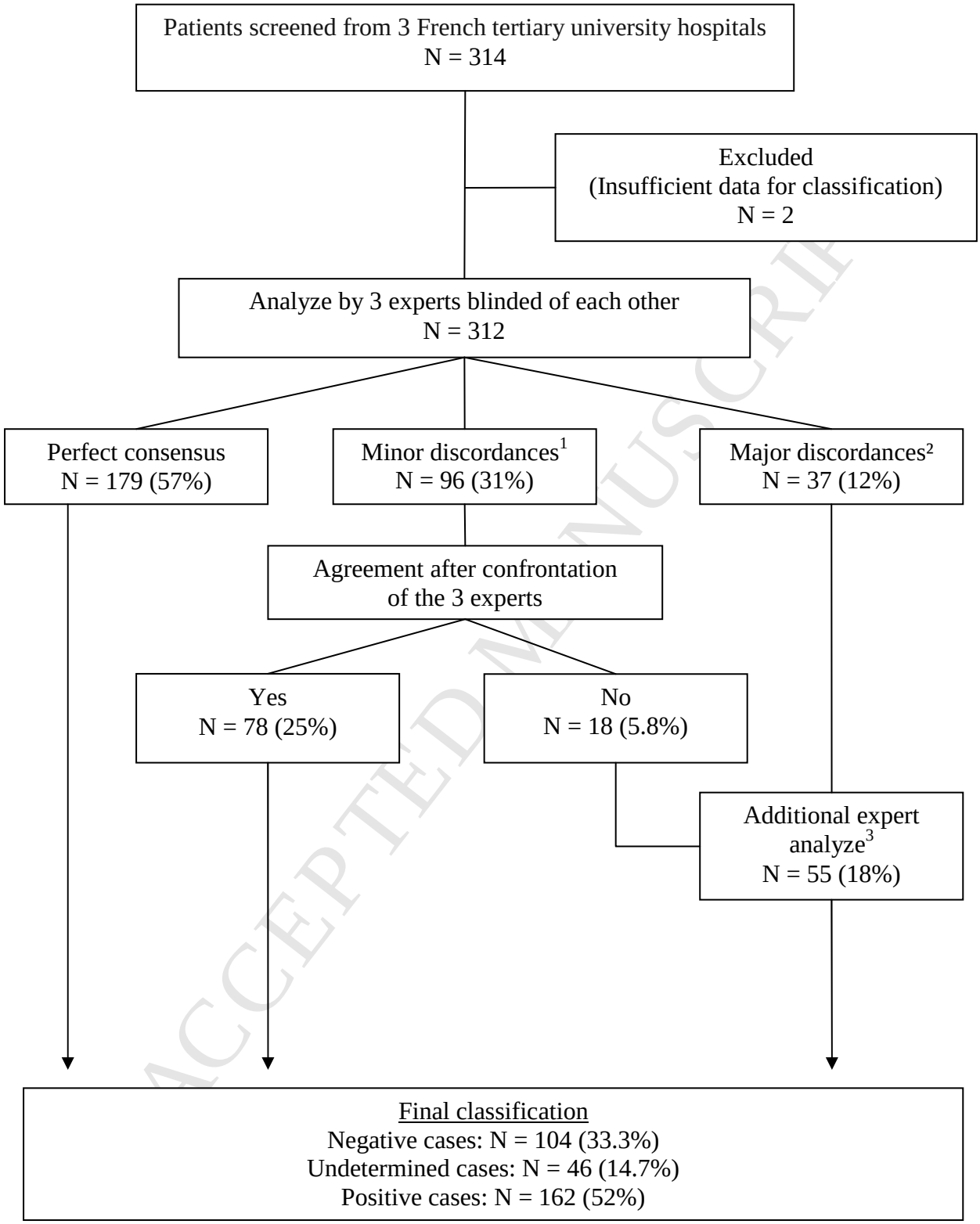
HIV: human immunodeficiency virus, CMV: cytomegalovirus, EBV: Epstein-Barr virus, HSV: herpes simplex virus, SLE: systemic lupus erythematosus

[1] toxoplasmosis, leishmaniosis or plasmodium falciparum

[2] Pneumocystis jirovecii or Candida albicans

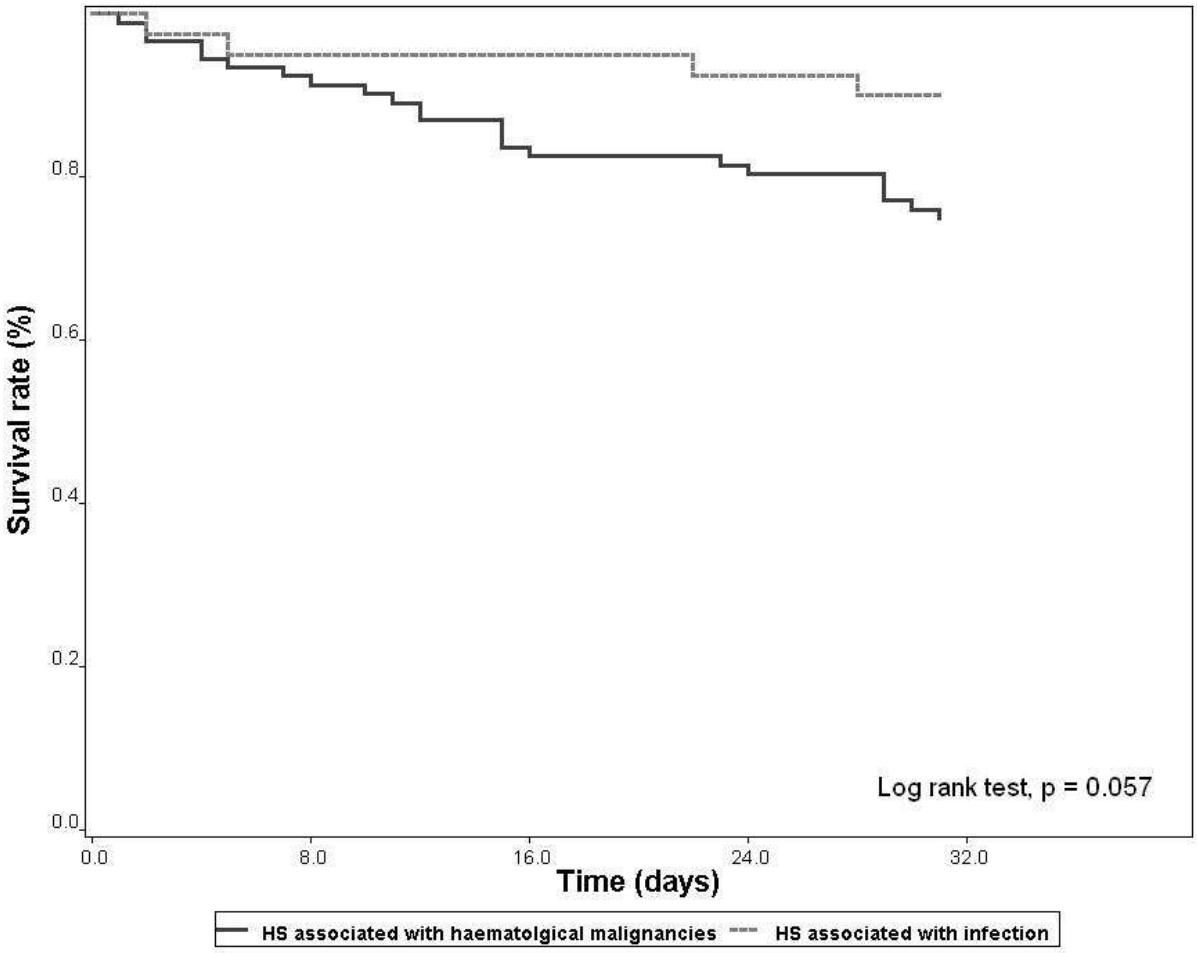
[3] Myositis (n = 2), vasculitis (n = 2), relapsing polychondritis (n = 1)

Figure 1: classification of patients



[1] Positive/undetermined and undetermined/negative classifications were considered as minor discordances
[2] Positive/negative classifications were considered as major discordances
[3] Agreement of 3 out the 4 experts was considered satisfying. If it was not reached, patients were classified undetermined cases (n = 8)

Figure 2: Survival curves for patients with hemophagocytic syndrome (HS) associated with haematological malignancies and infections



Clinical significance

- Only 70 % of patients with hemophagocytic syndrome had hemophagocytosis features on bone marrow aspiration.
- Nearly half of the patients have a known immunosuppression. All the causes of immunosuppression identified led to defects in cellular immunity.
- Hematological malignancies, particularly non-Hodgkin lymphomas, were the main diseases associated with hemophagocytic syndrome.
- Mortality rate within one month after diagnosis was 20%. Patients with haematological malignancies-associated hemophagocytic syndrome have a poorer early outcome than those with underlying infection.