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Characteristics and prognosis of *Herpesviridae*-related pneumonia in critically ill burn patients

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ARTICLE INFO

Article history:
Accepted 13 September 2021

Keywords:
Burn
Ventilator associated pneumonia
Herpes simplex viridae
SOFA score

ABSTRACT

Background: The aim of this study was to describe the prevalence, characteristics and outcome of critically burn patients with pulmonary HSV reactivation.
Methods: Retrospective, single-center cohort study in a burn critical care unit in a tertiary center, including all consecutive severely burn patients with bronchoalveolar lavage performed for pneumoniae suspicion and screened for HSV from January 2013 and April 2017. We used logistic regression to identify factors associated with HSV reactivation and outcomes.
Results: 94 patients were included, mean age was 51 (39–64) years; median total body surface area burned was 36 (25–54)% and ICU mortality 38%. Fifty-five patients (59%) had pulmonary HSV reactivation and 30 (55%) were treated with acyclovir. Patients with HSV reactivation were more severely ill with higher SOFA score at admission compared to patient without HSV reactivation (6 [3–8] vs. 2 [1–4], $p < 0.0001$ respectively). In multivariate analysis, sex, SOFA score at admission and smoke inhalation were significantly associated with HSV

Abbreviations: HSV, Herpes simplex virus; ICU, intensive care unit; BAL, broncho alveolar lavage; VAP, ventilator associated pneumonia; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; BMI, body mass index; TBSA, total body surface area; BSA, body surface area; SAPS II, simplified acute physiology score II; ABSI, abbreviated burn severity index; UBS, unit burn standard; HLA-DR, human leucocyte antigen DR; AUROC, area under the receiver operating characteristic.

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https://doi.org/10.1016/j.burns.2021.09.009

reactivation. Only septic shock was associated with 90-day mortality when HSV reactivation was not.

Conclusions: Pulmonary HSV reactivation is frequent among severely ill burn patients. Initial severity and smoke inhalation are risk factors. Antiviral treatment was not associated with outcome.

1. Introduction

Herpes simplex virus (HSV) is a common DNA virus for which the majority of the population becomes seropositive by age of 30 [1,2]. HSV resides latently in sensory neurons and reactivates in state of reduced immunocompetence [3]. Probably due to immune paralysis, HSV-1 can reactivate after burn injury [4,5]. HSV reactivation can lead to skin graft lysis and pneumoniae [4]. Whether or not those reactivations are responsible for morbidity or mortality remains controversial [6–8]. In non-burn intensive care unit (ICU) patients, a high load of HSV-1 has been associated with an increased mortality [9]. In a recent meta-analysis including 12 studies, patients with HSV reactivation had a higher mortality compared to patients without (odds ratio 1.8, 95% CI 1.2–2.6, p = 0.001) [10]. In a recent retrospective study, Schuierer et *al.* observed that in patients with high load of HSV ($>10^5$ HSV copies/mL) in bronchoalveolar lavage (BAL), ICU survival was higher in patients treated with acyclovir [11]. Factors associated with HSV-1 reactivation and the association between HSV-1 and outcome remains largely unknown in burn patients. Therefore, the main objective of this retrospective study was to describe the characteristics and outcomes of HSV-1 reactivation among burn patients.

2. Patients and methods

2.1. Study design and population

We conducted a single-center cohort study in the Burn Unit of Saint Louis Hospital (Assistance Publique Hôpitaux de Paris), Paris, France. The study was approved by our local ethic committee (PRONOBURN study, comité de protection des personnes IV, St-Louis Hospital; Institutional Review Board 00003835, protocol 2013/17NICB). Medical records of the patients admitted to our intensive care burn unit (ICBU) between January 2013 and April 2017 were screened.

All burn patients meeting the following criteria were included in the study: burn patients with a TBSA burned ≥15%, under mechanical ventilation with a BAL for suspicion of ventilator associated pneumonia (VAP) and tested for herpes simplex virus 1 and 2. Fiberoptic bronchoscopy with realisation of BAL was performed in every patient as soon as a VAP was suspected (*i.e.* temperature of at least 38.3 °C, purulent tracheal secretions, a new pulmonary infiltrate, or progression of an existing infiltrate) [12].

2.2. Main outcomes measures

The aim of this study was to describe the factors associated with lung HSV-1 reactivation.

The secondary objective was to assess whether pulmonary HSV reactivation or treatment was associated with outcome (*i.e.,* 90-day mortality, acute respiratory distress syndrome [ARDS] and acute kidney injury [AKI]) in severely burn patient. We choose to evaluate AKI as an outcome because of the potential association between treatment with IV acyclovir and development of AKI [13].

2.3. Data collection

The following data have been collected: age, sex, body mass index (BMI), total body surface area (TBSA), full-thickness body surface area (BSA) burned, mechanism of injury and patients' characteristics, Simplified Acute Physiology Score II (SAPS II) [14], Abbreviated Burn Severity Index (ABSI) [15], Unit Burn Standard (UBS) [16], Sequential organ failure assessment (SOFA) score [17] at admission and the day of the BAL, septic shock the day of BAL, bacterial pneumonia the day of BAL, acute kidney injury [18], nephrotoxic treatment or procedure (*i.e.,* CT-scan with injection, arteriography, aminoglycoside, glycopeptide, amphotericin B), 28 and 90-day mortality, and biological parameter including Human leucocyte antigen DR (HLA-DR), PaO2/FiO2. Molecular detection and quantification of HSV-1 and HSV-2 in BAL and/or plasma was carried out after automated DNA extraction with QiaSymphony system (Qiagen, Hilden, Germany) with the RealStar HSVPCR kit 1.0 (AltonaDiagnostics, Hamburg, Germany) on a Rotor-Gene-Q thermocycler (Qiagen) according to the manufacturer's recommendations.

2.4. Definitions

Acute respiratory distress syndrome was define according to the Berlin definition [19]. AKI was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [20] during the first 7 days after admission. Admission Screat (Screatadmin) was used as baseline Screat. A definition of severe burn has recently been proposed by French experts [21].

2.5. Patient management

Patients were resuscitated according to the Saint Louis Hospital Intensive Care Burn Unit resuscitation protocol described elsewhere [22] and followed the recommendation of the French society of Anesthesiology and Intensive Care [21]. We use early excision (*i.e.,* within 5 days of burn injury, with

20% maximum TBSA for each procedure) when the patient is deemed hemodynamically stable. Early enteral nutrition vitamins and oligo elements (selenium, Zn, Cu) supplements are used, adjusted on indirect calorimetry and vitamins/oligo elements plasma concentration. Furthermore, first used topical antimicrobial agent are flamazine and/or sulfamylon® and after the first surgery, topical antimicrobial agent are adjusted to the bacterial skin colonization, assessed every 48 h during the realization of the dressing. Patients were ventilated as follows: tidal volume was limited to 6–7 mL/Kg to maintain an inspiratory plateau pressure of less than 30 cmH_2O and a transpulmonary driving pressure <15 cmH_2O.

Patients with suspected VAP have a pulmonary sputum sample; the choice of the type of sampling (tracheal or bronchial aspiration or BAL) was left to clinician discretion. Antimicrobial therapy was started immediately after BAL realization in case of ARDS or septic shock. The antimicrobial therapy was secondarily adapted to Gram stain result and to bacterial susceptibility testing according to guidelines [23]. Plasma samples were collected for HSV detection when BAL were positive for HSV.

Pulmonary HSV reactivation was defined as positive PCR in the BAL. Treatment of HSV reactivation was decided in a multidisciplinary daily meeting if patients were suspected of HSV pneumonia (defining as: PCR >5log in BAL and clinical or radiological sign of pneumonia with or/without bacterial pneumonia). HSV reactivations were treated with intravenous Aciclovir® (Zovirax, Arrow, Lyon, France) 10 mg/kg three times a day for 10–14 days.

2.6. *Statistical analysis*

Continuous variables are reported as mean and standard deviation (SD) or median (25–75 percentiles) as appropriate. Categorical variables are expressed as count (percentage). Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Student t-test or the Mann– Whitney U test as appropriate. Area under the receiver operating characteristic (AUROC) curve were calculated to assess the ability of SOFA at admission, ABSI, age and TBSA to predict HSV reactivation.

Variables associated with outcomes in univariate analysis were entered in a multivariable logistic regression model to identify the factors independently associated with the outcome. Considering the rule of thumb suggesting at least 5–10 events for each predictor variable included in the model [24], only variable with a p value <0.2 in univariate analysis and/or the most clinically relevant (i.e., factors associated with severity of the burn injury or previously identified factors

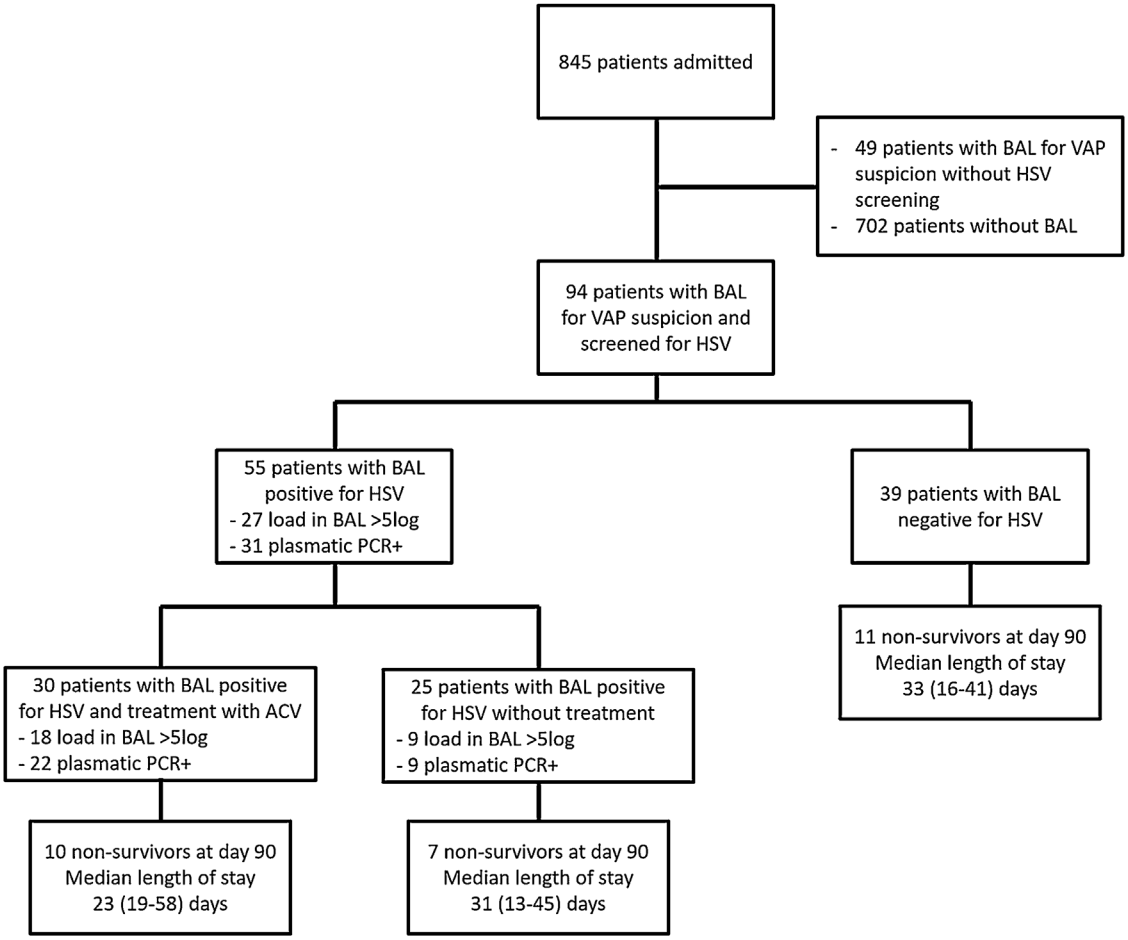

Fig. 1 – Flow chart.

associated with the risk of death) were included in the multivariate model. For HSV reactivation, SOFA score at admission, smoke inhalation, age and TBSA have been included in the multivariate analysis. For 90-day mortality, ABSI, SOFA score at admission, pulmonary HSV reactivation and septic shock the day of BAL have been included in the multivariate analysis. For AKI, ABSI, septic shock the day of BAL, pulmonary HSV reactivation and SOFA score at admission have been included in the multivariate analysis. For ARDS, SOFA score at admission, septic shock the day of the BAL, smoke inhalation, pulmonary HSV reactivation and bacterial pneumonia have been included in the multivariate analysis. In all comparisons, a p-value of less than 0.05 was considered for statistical significance. All analyses were performed on Medcalc (MedCalc software Ltd, Acacialaan 22 8400 Ostend Belgium).

3. Results

3.1. *Study population*

Between January 2013 and April 2017, 845 patients were admitted in our unit. Seven hundred and sixty seven patients did not meet the inclusion criteria. Ninety-four patients had a BAL for suspicion of VAP and HSV screening (Fig. 1), mean age

Table 1 – Patients characteristics between patients with pulmonary HSV reactivation and without.

Data	All patients N = 94	HSV negative N = 39	HSV reactivation N = 55	P
Demographic data:				
- Age (year)	51 (39–64)	53 (42–65)	51 (36–64)	0.52
- Male n (%)	66 (70)	31 (80)	35 (64)	0.15
- Body mass index (Kg/m^2)	25.8 (22.6–29)	24.6 (22.6–27.8)	26.1 (22.6–30.4)	0.37
Comorbidities n (%):				
- Hypertension	21 (22)	9 (23)	12 (22)	1
- Diabetes mellitus	9 (10)	4 (10)	5 (9)	1
- Chronic kidney disease	2 (2)	0 (0)	2 (4)	0.51
- Vascular disease	5 (5)	1 (3)	4 (7)	0.4
- Obesity	18 (19)	5 (13)	14 (25)	0.19
- Smoking	29 (31)	12 (31)	17 (31)	1
- Immunosuppression	3 (3)	2 (5)	1 (2)	0.57
Burn type n (%):				
- Thermal	92 (98)	39 (100)	53 (96)	0.51
- Electrical	0 (0)	0 (0)	0 (0)	1
- Chemical	2 (2)	0 (0)	2 (4)	0.51
Body Surface Area Burned (%):				
- Total	36 (25–54)	31 (18–54)	39 (25–55)	0.21
- Full-thickness	21 (10–42)	23 (8–41)	21 (10–45)	0.83
Death in ICU n (%)	33 (35)	12 (31)	21 (38)	0.52
Day of death	36 (19–78)	35 (16–44)	38 (20–84)	0.41
28-day mortality n (%)	13 (14)	5 (13)	8 (15)	1
90-day mortality n (%)	28 (30)	11 (28)	17 (31)	0.82
ICU length of stay in days	49 (35–78)	45 (36–60)	54 (32–79)	0.34
AKI n (%)	48 (51)	20 (51)	28 (51)	1
- Stade 1	13 (14)	8 (21)	5 (9)	0.20
- Stade 2	4 (4)	3 (8)	1 (2)	
- Stade 3	31 (33)	9 (23)	22 (40)	0.13
- RRT	30 (32)	9 (23)	21 (38)	0.19
Severity score:				
- SAPS II	34 (23–49)	32 (25–50)	35 (23–49)	0.98
- UBS	106 (55–180)	105 (46–179)	106 (59–183)	0.63
- ABSI	9 (7–11)	9 (7–11)	8 (6–11)	0.51
- SOFA (admission)	4 (2–7)	2 (1–4)	6 (3–8)	<0.0001
- SOFA (diagnosis)	7 (3–10)	8 (3–10)	7 (3–11)	0.77
Pre hospital management:				
- Delay between burn and admission in hours	4 (2.2–10.3)	5 (2.5–17)	3.8 (2–7.6)	0.55
- Volume of crystalloid between burn and admission in ml	2500 (1500–6000)	2500 (1500–6000)	2000 (1500–6250)	0.81
- Volume of crystalloid between burn and admission in ml/kg/%TBSA	18.2 (1.03–35.1)	19.8 (10.2–28.9)	16.3 (10.8–35.7)	0.63
Viral characteristics:				
- HSV1 n (%)			54 (98)	
- HSV2 n (%)			2 (4)	
- Positive plasmatic HSV n (%)			31 (56)	
- Plasmatic viral load in log			3.5 (0–4.2)	
- BAL viral load in log			4.8 (3.8–7.3)	

Table 1 (continued)

Data	All patients N = 94	HSV negative N = 39	HSV reactivation N = 55	P
BAL characteristics				
- Day of BAL	9 (6–18)	7 (3–17)	11 (7–20)	0.02
- BAL positive for bacteria n (%)	62 (66)	22 (56)	40 (73)	0.12
- Septic shock the day of BAL n (%)	41 (44)	19 (49)	22 (40)	0.53
Respiratory parameters:				
- MV n (%)	92 (98)	37 (95)	55 (100)	0.17
- Smoke inhalation n (%)	50 (53)	24 (62)	26 (47)	0.21
- Pulmonary burns n (%)	42 (45)	20 (51)	22 (40)	0.14
- ARDS n (%)	54 (57)	20 (51)	34 (62)	0.4
- Time of MV in days	25 (17–41)	20 (12–39)	26 (20–45)	0.05
- Days without MV	18 (0–35)	19 (0–34)	17 (0–37)	0.73
Radiological parameters:				
- Chest X-ray n (%)	93 (99)	38 (97)	55 (100)	0.4149
- CT scan n (%)	39 (42)	13 (33)	26 (47)	0.2065
- Radiological anomaly n (%)	92 (98)	39 (100)	53 (96)	0.5092
- Bilateral n (%)	74 (79)	31 (79)	43 (78)	1
- Pleural effusion n (%)	42 (45)	15 (38)	27 (49)	0.4002
- Pulmonary condensation n (%)	83 (88)	35 (90)	48 (87)	1
- Pulmonary abscess n (%)	3 (3)	0 (0)	3 (5)	0.2639
- Pulmonary ground glass n (%)	72 (77)	30 (77)	41 (74)	1

BMI: Body Mass Index; ICU: Intensive Care Unit; SAPS II: Simplified Acute Physiology Score 2; UBS: Unit Burn Standard; ABSI: Abbreviated Burn Severity Index; SOFA: sepsis related organ failure assessment; HSV: herpes simplex virus; PCR: polymerase chain reaction; BAL: Broncho alveolar lavage; HSV: herpes simplex virus; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome.

Data are expressed as median (CI95%) for continuous variables, and number (percentile) for discrete variables.

was 51 (39–64) years; median total body surface area burned was 36 (25–54) %, mean ABSI was 9 (7–11), all patient's characteristics are summarized in Table 1. Indications for mechanical ventilation were acute respiratory distress syndrome, deep and circular burn on the neck and/or symptoms of airway obstruction (*i.e.*, change in voice, stridor, and laryngeal dyspnea), and/or very extensive (*i.e.*, total burned body surface area > 40%).

3.2. *Description of the population with HSV reactivation*

Among the 94 patients with a BAL for VAP suspicion and HSV screening, 55 (56%) were positive for HSV with a minimum of 2.69 log in BAL (Table1). The median delay between admission and positive BAL for HSV was 11 (7–19) days.

Forty-nine percent of patients with HSV reactivation had HSV load in BAL > 5 log. Thirty patients with HSV reactivation were considered having a HSV pneumonia and treated with acyclovir. Among them, 18 (60%) had HSV load in BAL > 5 log. Among 55 patients with BAL positive for HSV, 42 patients (76%) had viremia (with no difference between patients with HSV load in BAL > or <5 log.

In univariate analysis, the characteristics of patients with or without pulmonary HSV reactivation was not significantly different except for SOFA score at admission (Table 1). Characteristics of patients with pulmonary HSV reactivation are summarized in Table 2. Fifty-four patients were positive for HSV1, two for HSV2 (one patient positive for HSV1 and 2 simultaneously). In patients with pulmonary HSV reactivation, 42 (76%) have been tested for HSV plasmatic reactivation. Among them, 31 (74%) had viremia. Fifteen (27%) of patients with pulmonary HSV reactivation had no bacteria in the culture of the BAL. Forty-five patients (82%) had a chest XRay the day of the BAL and 20 (36%) patients had a CT scan within the 24 h of the BAL. We found no difference in radiological characteristics between patients with and without HSV reactivation (with or without pneumonia) (Table 1). Clinical and pulmonary radiological characteristics of patients with HSV pneumonia are summarized in Table 2 and Table 3, respectively. Among patients with HSV pulmonary reactivation, patients treated with acyclovir had a higher TBSA, higher UBS and higher ABSI, and were longer on mechanical ventilation compared to not-treated patients (Table 2). We did not observe any differences in radiological characteristics between patients treated with acyclovir and not treated (Table 3). Acyclovir treatment was given more frequently in patients with higher severity and detection of HSV in plasma (Table 3). In patients with negative BAL for bacteria, we observed unspecific and heterogeneous imaging features (*i.e.*, condensation, pleural effusion, ground glass, micronodules) (Supplementary Fig. 1).

3.2.1. *Factors associated with HSV reactivation*

Factors associated with HSV reactivation are presented in Table 1. In patients with HSV reactivation, 38 (69%) had plasmatic HLA-DR the day of the BAL. In multivariate analysis, sex, SOFA score at admission and smoke inhalation, were associated with HSV reactivation (Table 4). A SOFA score at admission >4 predicted HSV reactivation with an AUROC of 0.76, a sensitivity of 66% and a specificity of 80% ($p < 0.0001$), whereas ABSI, age and TBSA did not (AUC = 0.51, 0.53, 0.56; respectively) (Supplementary Fig. 2).

Table 2 – Clinical characteristics of patients with HSV positive BAL between treated and not treated.

Data	All patients with HSV reactivation N = 55	Treated N = 30	Not treated N = 25	P
Demographic data:				
- Age (year)	51 (36–64)	47 (37–63)	51 (34–66)	0.5345
- Male n (%)	35 (64)	20 (67)	15 (60)	0.7790
- Body mass index (Kg/m^2)	26.1 (22.6–30.4)	24.7 (22.5–30.4)	27.7 (24.1–30)	0.3253
Comorbidities n (%):				
- Hypertension	12 (22)	5 (17)	7 (28)	0.3450
- Diabetes mellitus	5 (9)	2 (7)	3 (12)	0.6499
- Chronic kidney disease	2 (4)	1 (3)	1 (4)	1
- Vascular disease	4 (7)	1 (3)	3 (12)	0.3198
- Obesity	14 (25)	8 (27)	6 (24)	1
- Smoking	17 (31)	12 (40)	5 (20)	0.1472
- Immunosuppression	1 (2)	0 (0)	1 (4)	0.4545
Burn type n (%):				
- Thermal	53 (96)	30 (100)	23 (92)	0.2020
- Electrical	0 (0)	0 (0)	0 (0)	1
- Chemical	2 (4)	0 (0)	2 (8)	0.2020
Body Surface Area Burned (%):				
- Total	39 (25–55)	49 (32–61)	33 (24–40)	0.0239
- Full-thickness	21 (10–45)	29 (15–57)	14 (7–31)	0.0183
Death in ICU n (%)	21 (38)	13 (43)	8 (32)	0.4188
Day of death	38 (20–84)	23 (19–52)	31 (16–44)	
28-day mortality n (%)	8 (15)	5 (17)	3 (12)	0.7153
90-day mortality n (%)	17 (31)	10 (33)	7 (28)	0.7733
ICU length of stay in days	54 (32–79)	57 (32–97)	49 (36–67)	0.0945
AKI n (%)	28 (51)	17 (57)	11 (44)	0.51
- Stage 1	5 (9)	2 (7)	3 (12)	
- Stage 2	1 (2)	0 (0)	1 (4)	
- Stage 3	22 (40)	15 (50)	7 (28)	0.17
- RRT	21 (38)	15 (50)	6 (24)	0.20
Severity score:				
- SAPS II	35 (23–49)	41 (23–53)	31 (23–40)	0.0530
- UBS	106 (59–183)	132 (68–228)	74 (46–142)	0.0283
- ABSI	8 (6–11)	10 (8–12)	8 (7–9)	0.0211
- SOFA (admission)	6 (3–8)	6 (3–9)	6 (3–8)	0.3650
- SOFA (diagnosis)	7 (3–11)	7 (4–10)	8 (3–11)	0.8348
Respiratory parameters:				
- MV n (%)	55 (100)	30 (100)	25 (100)	1
- Smoke inhalation n (%)	26 (47)	15 (50)	11 (44)	0.7876
- Pulmonary burns n (%)	22 (40)	14 (47)	8 (32)	0.4074
- ARDS n (%)	34 (62)	22 (73)	12 (48)	0.0935
- Time of MV in days	26 (20–45)	31 (22–64)	23 (16–41)	0.0375
- Days without MV	17 (0–37)	16 (0–35)	22 (4–39)	0.8244

BMI: Body Mass Index; ICU: Intensive Care Unit; SAPS II: Simplified Acute Physiology Score 2; UBS: Unit Burn Standard; ABSI: Abbreviated Burn Severity Index; SOFA: sepsis related organ failure assessment; HSV: herpes simplex virus; PCR: polymerase chain reaction; BAL: Broncho alveolar lavage; HSV: herpes simplex virus; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome.
Data are expressed as median (CI95%) for continuous variables, and number (percentile) for discrete variables.

3.3. *Outcome*

3.3.1. *Factors associated with outcome*

Overall, 28 and 90-days mortality was 14% (N = 13) and 30% (N = 28) respectively (Table 5). In multivariate analysis, only a septic shock the day of the BAL was associated with mortality (Supplementary data Table 1).

Forty-eight patients (51%) developed an AKI during their ICU length of stay. In multivariate analysis, only ABSI and septic shock the day of the BAL were associated with the occurrence of AKI (Supplementary data Table 2).

Fifty-four (57%) patients developed an ARDS, in multivariate analysis, only smoke inhalation was associated with ARDS (Supplementary data Table 3).

In univariate analysis, patients with HSV reactivation had a higher length of stay in ICU (Table 1). In multivariate regression analysis including age, TBSA burned and HSV reactivation, only TBSA burned remained associated with ICU length of stay ($r = 0.2451$; $p = 0.0186$). Non survivors had higher plasmatic viral load (Table 5). However, 90-day mortality was not different between patients with HSV load >5log vs those with HSV load < 5log (33% vs. 29%, respectively, p = 1).

Table 3 – Biological and radiological characteristics of patients with HSV positive BAL between treated and not treated.

Data	All patients with HSV reactivation N = 55	Treated N = 30	Not treated N = 25	P
Clinical characteristics				
Biological and ventilatory characteristics				
- HLA-DR	3869 (2341–7482)	3628 (2926–7019)	5171 (1843–8724)	0.8396
- PCT	2.25 (0.69–5.26)	2.1 (0.62–5.27)	2.52 (0.96–5.26)	0.5105
- PaO2/FiO2	194 (119–287)	166 (121–280)	223 (105–318)	0.4482
- PEEP (mmHg)	8 (6–11)	10 (6–12)	8 (6–10)	0.3459
Viral characteristics				
- HSV1 n (%)	54 (98)	30 (100)	24 (96)	0.4545
- HSV2 n (%)	2 (4)	1 (3)	1 (4)	1
- Positive plasmatic HSV n (%)	31 (56)	22 (73)	9 (36)	0.0071
- Plasmatic viral load log	3.5 (0–4.2)	3.5 (3.1–4.2)	2.2 (0–4.3)	0.2360
- BAL viral load log	4.8 (3.8–7.3)	5.6 (4.4–7.5)	4 (3.2–7.3)	0.1461
BAL characteristics				
- Day of BAL	11 (7–20)	11 (7–15)	12 (7–24)	0.5215
- BAL positive for bacteria n (%)	40 (73)	22 (73)	18 (72)	1
- Septic shock the day of BAL n (%)	22 (40)	10 (33)	12 (48)	0.2865
- BAL HSV load in log	5.2 (3.9–7.4)	5.6 (4.4–7.4)	4 (3.2–7.3)	0.1461
- BAL HSV load >5log n (%)	27 (49)	18 (60)	9 (36)	0.1331
Radiological parameters:				
- Chest Xray n (%)	55 (100)	30 (100)	25 (100)	1
- CT scan n (%)	26 (47)	14 (47)	8 (32)	0.4074
- Radiological anomaly n (%)	53 (96)	29 (97)	24 (96)	1
- Bilateral n (%)	43 (78)	26 (87)	17 (68)	0.1139
- Pleural effusion n (%)	27 (49)	14 (47)	13 (52)	0.7891
- Pulmonary condensation n (%)	48 (87)	27 (90)	21 (84)	0.6894
- Pulmonary abscess n (%)	3 (5)	2 (7)	1 (4)	1
- Pulmonary ground glass n (%)	41 (74)	25 (83)	17 (68)	0.2159

HLA-DR: human leucocyte antigen DR; PCT: procalcitonin; BMI: Body Mass Index; ICU: Intensive Care Unit; SAPS II: Simplified Acute Physiology Score 2; UBS: Unit Burn Standard; ABSI: Abbreviated Burn Severity Index; SOFA: sepsis related organ failure assessment; HSV: herpes simplex virus; PCR: polymerase chain reaction; BAL: Broncho alveolar lavage; HSV: herpes simplex virus; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome.

Data are expressed as median (CI95%) for continuous variables, and number (percentile) for discrete variables.

Table 4 – Multivariable analysis of factors associated with HSV reactivation.

Variable	Odds ratio	95% CI	P
Sex	0.2660	0.0812 to 0.8711	0.0287
SOFA on admission	1.4895	1.2284 to 1.8062	0.0001
TBSA burned %	1.0054	0.9833 to 1.0280	0.6361
Smoke inhalation	0.3161	0.1119 to 0.8930	0.0297

58% of patients with HSV reactivation had a second BAL (median time between the 2 BAL was 6 (4–15) days. HSV load decreased in 20/32 (63%) patients with a decrease in HSV load, 15/23 in patients treated with acyclovir vs 5/9 patients not treated (median decreased in load 2.28 [1.07–5.25] and 3.25 [2.35–3.83] log in treated and non-treated respectively, p = 0.8).

4. Discussion

Pulmonary HSV reactivation is frequent in severely ill burn patients and was observed in more than half of patients with suspected VAP screened for HSV. Factors associated with HSV reactivation were the sex, the SOFA score at admission and smoke inhalation.

We did not find any differences in terms of prognosis between patients with or without HSV pulmonary reactivation, and no association between outcomes among patients HSV with pulmonary reactivation and treated with acyclovir.

Bruynseels et al. [25] reported that 22% of non-selected ICU patients had HSV reactivation in the throat, whereas Luyt et al. [26] observed HSV detection in the upper and lower respiratory tract in 54% and 64% of cases respectively, in a prospective, observational study among medical ICU patients. In our study, we observed a 56% prevalence of HSV pulmonary reactivation. We can't however conclude between reactivation or primary infection due to lack of HSV IgG serum titers at admission [27–29]. However, one can expect that seroprevalence in this population is closed to the one observed in the general population.

Radiological findings were totally unspecific and in accordance with observations in the literature. Indeed, in small series of immunocompromised patients with isolated HSV pneumonia, diffuse ground glass, consolidation and pleural effusion are the most common observed radiological abnormalities [30,31].

Table 5 – Patients characteristics between survivors and non survivors.

Data	All patients N = 94	Survivors N = 66	Non-Survivors N = 28	P
Demographic data:				
- Age (year)	51 (39–64)	49 (35–64)	59 (42–68)	0.0951
- Male n (%)	66 (70)	45 (67)	21 (75)	0.8645
- Body mass index (Kg/m^2)	25.8 (22.6–29)	24.7 (22.7–28.3)	27.7 (22.6–30.8)	0.2149
Comorbidities n (%):				
- Hypertension	21 (22)	13 (19)	8 (29)	0.4185
- Diabetes mellitus	9 (10)	4 (6)	5 (18)	0.1202
- Chronic kidney disease	2 (2)	1 (1)	1 (4)	0.5092
- Vascular disease	5 (5)	3 (4)	2 (7)	0.6323
- Obesity	18 (19)	11 (17)	7 (25)	0.3950
- Smoking	29 (31)	18 (27)	11 (39)	0.2302
- Immunosuppression	3 (3)	2 (3)	1 (4)	1
Burn type n (%):				
- Thermal	92 (98)	64 (97)	28 (100)	0.3184
- Electrical	0 (0)	0 (0)	0 (0)	1
- Chemical	2 (2)	2 (3)	0 (0)	1
Body Surface Area Burned (%):				
- Total	36 (25–54)	36 (26–50)	35 (19–61)	0.5903
- Full-thickness	21 (10–42)	20 (8–35)	27 (15–57)	0.0928
Death in ICU n (%)	33 (35)			
Day of death	36 (19–78)			
28-day mortality n (%)	13 (14)			
90-day mortality n (%)	28 (30)			
ICU length of stay in days	49 (35–78)	57 (42–93)	29 (18–44)	<0.0001
AKI n (%)	48 (51)	23 (34)	25 (89)	<0.0001
- Stade 1	13 (14)	9 (13)	4 (14)	1
- Stade 2	4 (4)	2 (3)	2 (7)	0.5798
- Stade 3	31 (33)	12 (18)	19 (67)	<0.0001
- RRT	30 (32)	12 (18)	18 (64)	<0.0001
Severity score:				
- SAPS II	34 (23–49)	31 (23–45)	40 (28–54)	0.0672
- UBS	106 (55–180)	97 (48–152)	115 (63–232)	0.1514
- ABSI	9 (7–11)	9 (7–10)	9.5 (7–12)	0.0898
- SOFA (admission)	4 (2–7)	3 (2–6)	5 (1.5–9)	0.0282
- SOFA (diagnosis)	7 (3–10)	4 (3–8)	9.5 (8–13)	<0.0001
Pre hospital management:				
- Delay between burn and admission in hours	4 (2.2–10.3)	3.3 (2–9)	6 (2.5–52)	0.0862
- Volume of crystalloid between burn and admission in ml	2500 (1500–6000)	2500 (1500–6250)	3500 (1500–6125)	0.5933
- Volume of crystalloid between burn and admission in ml/kg/%TBSA	18.2 (1.03–35.1)	19 (10.8–34.8)	14 (8.7–36.7)	0.6433
Viral characteristics				
- HSV1 n (%)	54 (57)	38 (58)	16 (57)	1
- HSV2 n (%)	2 (2)	1 (2)	1 (4)	0.5092
- Positive plasmatic HSV n (%)	31 (33)	19 (29)	12 (43)	0.2388
- Plasmatic viral load log	3.4 (0–4.1)	3 (0–3.75)	4.2 (3.3–4.6)	0.0270
- BAL viral load log	4.6 (3.2–7.1)	4.4 (3.2–7.1)	4.8 (0–7.4)	0.9308
BAL characteristics				
- HSV reactivation n (%)	55 (17)	38 (57)	17 (61)	0.8224
- Day of BAL	9 (6–18)	8 (5–15)	12 (8–28)	0.2813
- BAL positive for bacteria n (%)	62 (66)	44 (66)	18 (64)	0.8167
- Septic shock the day of BAL n (%)	41 (44)	19 (28)	22 (79)	<0.0001
- HSV treatment n (%)	30 (32)	20 (30)	10 (36)	0.6343
Respiratory parameters:				
- MV n (%)	92 (98)	65 (97)	27 (96)	1
- Smoke inhalation n (%)	50 (53)	32 (48)	18 (64)	0.1816
- Pulmonary burns n (%)	42 (45)	27 (40)	15 (54)	0.2686
- ARDS n (%)	54 (57)	31 (46)	23 (82)	0.0026
- Time of MV in days	25 (17–41)	25 (16–45)	29 (18–39)	0.1701
- Days without MV	18 (0–35)	25 (13–40)	0 (0–0)	<0.0001

BMI: Body Mass Index; ICU: Intensive Care Unit; SAPS II: Simplified Acute Physiology Score 2; UBS: Unit Burn Standard; ABSI: Abbreviated Burn Severity Index; SOFA: sepsis related organ failure assessment; HSV: herpes simplex virus; PCR: polymerase chain reaction; BAL: Broncho alveolar lavage; HSV: herpes simplex virus; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; RRT: renal replacement therapy.

Data are expressed as median (CI95%) for continuous variables, and number (percentile) for discrete variables.

In multivariate analysis, factors associated with HSV reactivation were sex, smoke inhalation and SOFA score at admission. The association with sex could be explain by an increased seroprevalence of HSV-1 in female compared to men [32]. Smoke inhalation is associated with an early anti-inflammatory response with an increase of IL-1 receptor antagonist even after adjustment on TBSA burned [33]. IL-1 has been shown to be involved in the immunological response against HSV-1 infection [34], therefore an inhibition of IL-1 may be associated with an increased risk of HSV pulmonary reactivation in patients with smoke inhalation injury. We observed an association between SOFA score at admission and HSV reactivation. This observation might help identify patients at higher risk when screening for HSV infections during the ICU course, more severe patients being at higher risk [26].

TBSA was not associated with the risk of HSV infection. Burn injuries have been associated with innate and adaptive immune dysfunction [35]. Our study mostly included very severe patients with a median TBSA of 36% probably explaining the lack of significant association with HSV infections. We however observed a higher plasma viral load in more severe patients. In burn patients with 30% of TBSA or more, several genes implicated in antigen presentation and T-cell proliferation are down regulated [35], this immune dysregulation could increase the risk of viral reactivation [36,37].

Only one study found an association between mortality and HSV infections in burn patients. In this autopsy series of 54 burn patients [38], the authors described that HSV pneumonia was associated with ARDS and death. Such results were not replicated by others who did not observed an association between HSV pneumonia and outcome [27–29].

In a retrospective study, Sen et al. [29] observed an association between cutaneous HSV reactivation and length of stay (adjusted on TBSA and age) and between HSV reactivation and duration of mechanical ventilation (adjusted on TBSA and age). In our study, we did not observe any association between pulmonary HSV reactivation or treatment of pulmonary HSV reactivation and length of stay in the ICU. Indeed, in severely burn patients, length of stay in ICU is largely driven by the % of TBSA burned, therefore it is unlikely that HSV reactivation could be responsible for an increased length of stay.

In a retrospective study, Fidler et al. [28] described intravenous acyclovir therapy in 15 HSV-1 positive cases. In one patient, worsening renal function was suspected to be related to the intravenous antiviral treatment. No benefits of the acyclovir treatment was observed on other outcomes. This result is in accordance with our study where we did not find any outcome differences between patients treated with acyclovir or not. Whether treatment impacts patient-centered outcome should be tested in randomized controlled trials.

4.1. *Interpretation and perspective*

The prevalence of respiratory reactivation in severely burn patients is not known and should be evaluated in a prospective observational study as well as its association with outcome. A recent meta-analysis suggested a beneficial effect of acyclovir treatment on 30-days mortality (RR 0.75 [0.59, 0.94]) but not with ICU mortality (RR 0.73 [0.51, 1.05]) with a low to very low level of evidence, suggesting that large RCT should be performed to identify which patient may benefit the most from antiviral therapy [39].

4.2. *Limitations*

Our study has some limitations. First, this was an observational study, and thus it describes a prevalence of 50% of HSV pulmonary reactivation but not necessarily pneumonia since we did not performed biopsy for pathological analyses. Second, the criteria to initiate the treatments were not standardized. Third, the study is likely underpowered to account for all potential cofounding factors that can impact burn patients' outcomes (*e.g.*, wound care, surgical treatments, nutrition). Finally, it was a single center study. This may limit the generalizability of the results. However, our results are in accordance with the literature.

5. Conclusion

In this retrospective study, we observed that pulmonary HSV reactivation is frequent. Smoke inhalation, sex and severity score at admission are associated with pulmonary HSV reactivation. Imaging findings were totally aspecific. Pulmonary HSV reactivation and treatment were not associated with outcome in severely burn patients. However, larger multicentric cohorts and international trial are needed to confirm these results.

Conflict of interest

All authors have no conflict of interests to declare.

Authors' contribution

FD collected data, performed analysis and interpretation of the data and drafted the manuscript.

JR collected data, contributed to interpretation of the data and to drafting the manuscript.

MC collected data, contributed to interpretation of the data and to drafting the manuscript.

AF collected data, contributed to interpretation of the data and to drafting the manuscript.

AC contributed to interpretation of the data and to drafting the manuscript.

SS collected data, contributed to interpretation of the data and to drafting the manuscript.

MB collected data, contributed to interpretation of the data and to drafting the manuscript.

AM conceived the study, contributed to interpretation of the data and to drafting the manuscript.

MS performed HSV PCR, contributed to interpretation of the data and to drafting the manuscript.

JLG performed HSV PCR, contributed to interpretation of the data and to drafting the manuscript.

ML collected data, contributed to interpretation of the data and to drafting the manuscript.

KS collected data, contributed to interpretation of the data and to drafting the manuscript.

MC collected data, contributed to interpretation of the data and to drafting the manuscript.

ML conceived the study, performed interpretation of the data and drafted the manuscript.

All authors read and approved the final manuscript.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.burns.2021.09.009.

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