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Long-term Quality of Life in Adult Patients Surviving Purpura Fulminans: An Exposed-Unexposed Multicenter Cohort Study

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Background. Long-term health-related quality of life (HR-QOL) of patients surviving the acute phase of purpura fulminans (PF) has not been evaluated.

Methods. This was a French multicenter exposed-unexposed cohort study enrolling patients admitted in 55 intensive care units (ICUs) for PF from 2010 to 2016. Adult patients surviving the acute phase of PF (exposed group) were matched 1:1 for age, sex, and Simplified Acute Physiology Score II with septic shock survivors (unexposed group). HR-QOL was assessed during a phone interview using the 36-Item Short-Form Health Survey (SF-36) questionnaire, the Hospital Anxiety and Depression (HAD) scale, the Impact of Event Scale-Revised (IES-R), and the activity of daily living (ADL) and instrumental ADL (IADL) scales. The primary outcome measure was the physical component summary (PCS) of the SF-36 questionnaire.

Results. Thirty-seven survivors of PF and 37 of septic shock were phone-interviewed at 55 (interquartile range [IQR], 35–83) months and 44 (IQR, 35–72) months, respectively, of ICU discharge ($P = .23$). The PCS of the SF-36 was not significantly different between exposed and unexposed patients (median, 47 [IQR, 36–53] vs 54 [IQR, 36–57]; $P = .18$). There was also no significant difference between groups regarding the mental component summary of the SF-36, and the HAD, IES-R, ADL and IADL scales. Among the 37 exposed patients, those who required limb amputation ($n = 12/37$ [32%]) exhibited lower PCS (34 [IQR, 24–38] vs 52 [IQR, 42–56]; $P = .001$) and IADL scores (7 [IQR, 4–8] vs 8 [IQR, 7–8]; $P = .021$) compared with nonamputated patients.

Conclusions. Long-term HR-QOL does not differ between patients surviving PF and those surviving septic shock unrelated to PF. Amputated patients have an impaired physical HR-QOL but a preserved mental health.

Clinical Trials Registration. NCT03216577.

Keywords. purpura fulminans; septic shock; quality of life; SF-36; outcome.

Purpura fulminans (PF) is a rare life-threatening infectious disease predominantly caused by *Neisseria meningitidis* and *Streptococcus pneumoniae* [1], and mainly affecting young and

healthy patients [1–3]. Despite prompt antibiotic administration and intensive care management, PF carries a high mortality [1–3]. Patients surviving to the early phase of PF are exposed to a high risk of serious sequelae related to extensive skin necrosis and acral gangrene, which commonly require limb amputations [1], a potential source of severe handicap leading to a decreased health-related quality of life (HR-QOL) of these young and previously healthy patients. Although well studied in children surviving meningococcal septic shock [4–9], no controlled study has assessed long-term HR-QOL in adult patients surviving the acute phase of PF. Whether HR-QOL of PF patients who

survived after an intensive care unit (ICU) hospitalization differs from that of patients who survived a septic shock unrelated to PF is unknown. Additionally, the impact of limb amputation on HR-QOL of PF patients surviving the acute phase of PF has never been assessed.

We aimed at comparing the long-term HR-QOL of patients who survived the acute phase of PF (exposed group) with that of patients with septic shock unrelated to PF (unexposed group) by using validated psychological instruments [10–14]. Among PF survivors, we also aimed at comparing HR-QOL between amputated and nonamputated patients.

METHODS AND PATIENTS

Patients

We performed a multicenter exposed-unexposed cohort study in 55 ICUs in France (see [Appendix](#)). Exposed patients were adult (≥ 18 years old) patients surviving an ICU hospitalization for an infectious PF occurring between 2010 and 2016. Infectious PF was defined by the association of a sudden and extensive purpura, whatever its causative microorganism, together with an acute circulatory failure needing vasopressor support [1–3]. PF-exposed patients were matched with PF-unexposed patients, defined as adult (≥ 18 years old) patients surviving to an ICU hospitalization for a septic shock unrelated to PF during the same time frame. Unexposed patients were recruited from 2 prospective studies on sepsis [15, 16], and were matched to exposed patients for age (± 10 years), Simplified Acute Physiology Score (SAPS) II (± 20 points), and sex, using a 1:1 matching procedure.

Phone Interviews

Both exposed and unexposed patients were contacted by an introductory letter explaining the nature of the study. Phone interviews were conducted from November 2017 to March 2018 by 2 dedicated nurses using an electronic standardized form. The 2 nurses conducting phone interviews were blinded to the exposed or nonexposed status of the patients.

Data Collection

In exposed and unexposed patients, the following data were retrospectively [1] collected: age, sex, main comorbidities, SAPS II [17], portal of entry of sepsis in patients with septic shock unrelated to PF [15, 16], empirical antibiotic treatment, microbiological documentation, need for invasive mechanical ventilation, and durations of vasopressor support and ICU stay. To assess patient-reported outcomes, the following questionnaires were administered to exposed and nonexposed patients during phone interviews: (i) the validated French version of the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) questionnaire [14, 18]; (ii) the Hospital Anxiety and Depression (HAD) scale [13, 19]; (iii) the Impact of Event Scale-Revised (IES-R) [12, 20]; (iv) the level of independence evaluated with the activities of daily living (ADL)

[10]; (v) the instrumental activities of daily living (IADL) scales [11]; (v) a self-assessed global quality of life evaluated with a quantitative score ranging from 0 (worst value) to 100 (best value); and (vi) a selection of relevant individual and contextual determinants of HR-QOL in this population.

Outcome Measures

The primary outcome measure was the Physical Component Summary (PCS) from the SF-36 questionnaire, compared between exposed (PF survivors) and unexposed (matched septic shock survivors) patients. The SF-36 is a validated, generic HR-QOL questionnaire [14, 21, 22]. It comprises 36 items assessing 8 HR-QOL dimensions, covering physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Physical and mental summary components (PCS and MCS, respectively) constitute aggregates of the 8 individual dimensions to provide summary scores from physically and mentally oriented subscales using weights updated for the French population.

Secondary outcome measures included comparisons between exposed and unexposed patients and comparisons between PF survivors who underwent amputation or not.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR) or mean and standard deviation (SD) and compared as appropriate. Categorical variables are reported as numbers and percentages (95% confidence interval [CI]) and compared as appropriate. Differences of distribution in categorical variables were analyzed using the Pearson χ^2 or the Fisher exact test. Continuous variables were compared using the Student *t* test or the Wilcoxon-Mann-Whitney test, as appropriate. Comparisons of patient-centered outcomes between matched patients were performed using a mixed logistic regression with adjustment for age, SAPS II, and pair as a random effect. SF-36 subdimensions were expressed as raw values (normalized on a 0–100 scale) and age-sex standardized values, using reference values of the French population [18], and expressed as SD (*z* scores). SF-36 aggregate components (ie, PCS and MCS) were computed as recommended [23] and also expressed either on a normalized scale centered on 50 representing the population norm (ie, values $>$ or $<$ 50 reflecting values higher or lower than age-sex standardized French values) or as age-sex standardized values (*z* scores). All tests were 2-tailed and $P < .05$ was considered significant. Missing data were not replaced. Analyses were conducted using Stata version 13.1 software (StataCorp, College Station, Texas).

Ethical Considerations

This study was approved by the Institutional Review Board of the French Intensive Care Society in March 2016 (SRLF16-01). The investigators informed patients orally and with a written document. In accordance with French law, written informed consent was not required.

RESULTS

Characteristics of Exposed and Unexposed Patients

From 2000 to 2016, a total of 306 patients were admitted to one of the 55 participating ICUs for an infectious PF [1] with 144 patients being admitted between 2010 and 2016 (Figure 1). Among these, 78 (54%) survived to hospital discharge and were thus eligible for study inclusion. Thirty-four of these 78 patients were lost to follow-up, and 7 refused to participate in the phone survey, leaving 37 (47%) who agreed to participate and were matched with 37 patients who were admitted in the ICU during the same time period for a septic shock unrelated to PF (unexposed patients) and eventually discharged alive. Among the 37 exposed patients, 12 (32%) needed limb amputations with a median number of amputated limbs of 4 (IQR, 1–4). Of note, when compared with the 41 PF survivors of the cohort who were lost to follow-up or refused to participate (Figure 1), the 37 phone-interviewed patients had similar age (median, 39 [IQR, 23–55] vs 36 [IQR, 20–56] years; $P = .62$), sex ratio (male/female ratio: 25/16 vs 16/21; $P = .17$), SAPS II (51 [IQR, 36–62] vs 42 [IQR, 33–59]; $P = .23$), and rate of amputation (32% vs 32%; $P > .99$). Demographics, initial features, and characteristics of phone interviews for survivors of PF and septic shock unrelated to PF are detailed in Table 1. Because PF patients were systematically younger than septic shock patients, the matching procedure had to be relaxed regarding age (ie, ± 20 years); as a result, PF patients tended to be younger than septic shock patients; to limit

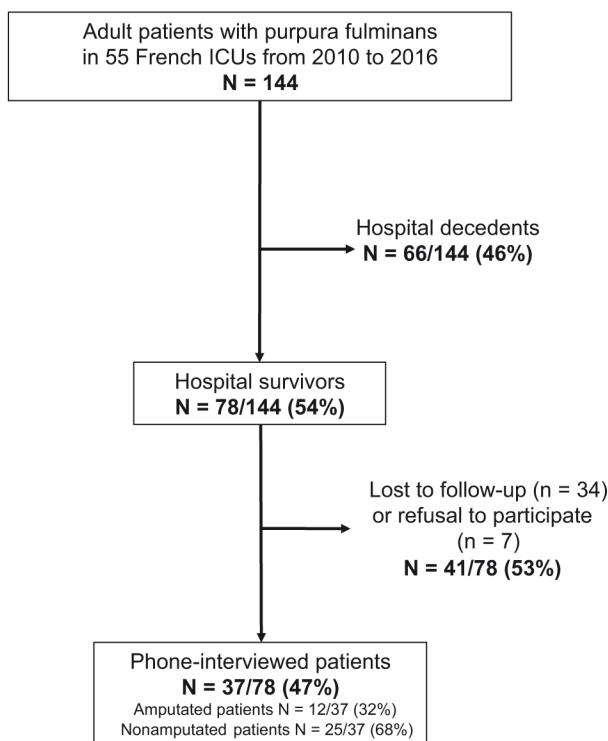


Figure 1. Study flowchart. Abbreviation: ICU, intensive care unit.

Table 1. Demographics, Initial Features, and Characteristics of Phone Interviews for Survivors of Purpura Fulminans (n = 37) and Septic Shock (n = 37)

Characteristic	Purpura Fulminans (n = 37)	Septic Shock (n = 37)	P Value
Matching procedure			
Age, y, median (IQR)	43 (25–61)	53 (37–63)	.054
Sex, male/female ^a	15/22	14/23	>.99
SAPS II, median (IQR)	42 (30–56)	32 (26–56)	.21
Patient characteristics			
Main comorbidities			
Asplenia/sickle cell disease	3 (8)	2 (5)	>.99
Cirrhosis	0 (0)	3 (8)	.24
Chronic cardiac failure	0 (0)	2 (5)	.49
Chronic lung disease	0 (0)	5 (13)	.054
Chronic kidney failure	0 (0)	2 (5)	>.99
Active solid cancer or malignant hemopathy	0 (0)	6 (16)	.025
Diabetes mellitus	1 (3)	8 (22)	.028
Obesity	1 (3)	10 (27)	.007
No comorbidity	27 (73)	12 (32)	<.001
Cause of septic shock/portal of entry			
Purpura fulminans	
<i>Neisseria meningitidis</i>	28 (76)	...	
<i>Streptococcus pneumoniae</i>	8 (21)	...	
Unknown	1 (3)	...	
Septic shock			
Respiratory tract	...	21 (57)	
Skin and soft tissue	...	7 (19)	
Urinary tract	...	6 (16)	
Digestive	...	1 (3)	
Other	...	2 (5)	
Adequate empirical antibiotic treatment	37 (100)	35 (94)	.47
Mechanical ventilation	28 (76)	27 (73)	.79
Duration of vasopressor support, d, median (IQR)	3 (3–5)	3 (2–4)	.21
Duration of ICU stay, d, median (IQR)	8 (4–18)	9 (4–24)	.98
Characteristics of the phone interview			
Delay between ICU discharge and interview, mo, median (IQR)	55 (35–83)	44 (35–72)	.23
Duration of the interview, min, median (IQR)	33 (25–40)	30 (25–44)	.86

P values for comparisons of categorical variables come from the Pearson χ^2 or the Fisher exact test, and for comparison of continuous variables, from the Wilcoxon-Mann-Whitney test. Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II.

^aOne male patient with purpura fulminans could only be matched with a female septic shock patient.

this selection bias, a systematic adjustment for age was done in the analysis. *P* values were further adjusted on SAPS II: although this variable was not significantly different between groups, the difference was clinically relevant, suggesting a residual selection bias. Of note, groups were comparable regarding the duration of vasopressor support, the proportion of adequate empirical antibiotic therapy, the time elapsed between ICU discharge and phone interview, duration of ICU stay, and need for mechanical ventilation (Table 1). The causative microorganisms retrieved in the unexposed group are detailed in Supplementary Table 1.

Primary Outcome

There was no significant difference between PF and septic shock survivors regarding the PCS aggregate score of the SF-36 questionnaire (Figure 2A and Supplementary Table 2), even when the age and SAPS II imbalances between groups were accounted for ($P = .18$). Yet, the age-sex standardized PCS of exposed patients was substantially lower than that of the reference population (SD, -0.63), although this difference was not statistically greater than that measured in unexposed patients

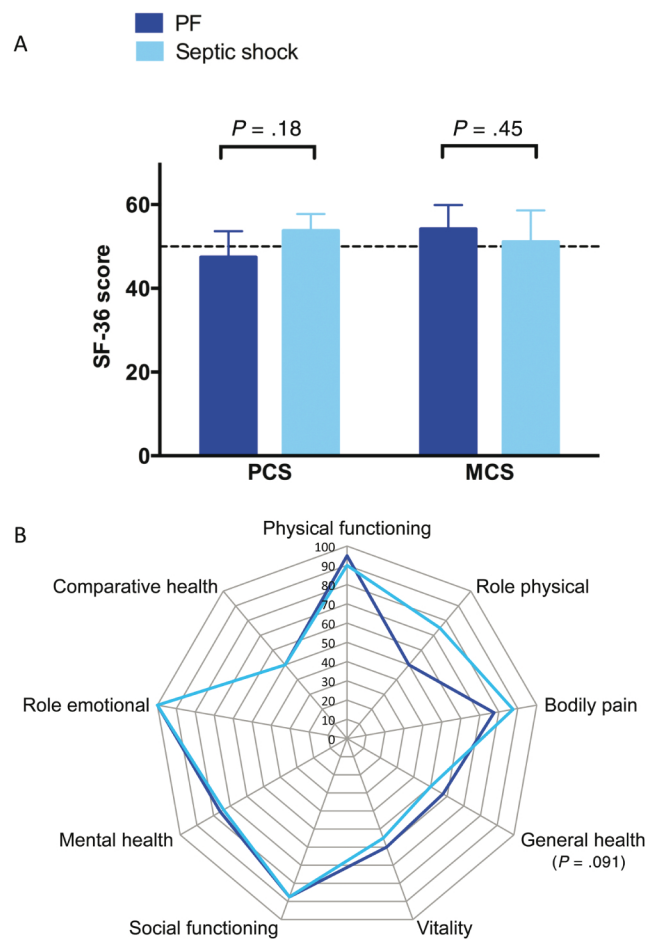


Figure 2. Results of the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) questionnaire in exposed (purpura fulminans survivors) and non-exposed (septic shock survivors) patients. *A*, Comparison of the Physical (PCS) and Mental (MCS) component summaries of the SF-36 questionnaire between patients surviving purpura fulminans (PF, dark blue) and patients surviving a septic shock from other cause (sky blue). Results are centered on the value of 50 (dashed line; values $>$ or $<$ 50 reflected values higher or lower than age-sex standardized French values). P values come from a mixed logistic regression with adjustment for age and pair as a random effect; *B*, Comparison of each subdomain of the SF-36 questionnaire between patients surviving purpura fulminans (PF, dark blue) and patients surviving a septic shock (sky blue). The “Physical functioning”, “Role physical”, “Bodily pain”, and “General health” subdimensions pertain to the PCS aggregate component, the “Vitality”, “Social functioning”, “Mental health”, and “Role emotional” subdimensions pertain to the MCS aggregate component, the “Health transition” subdimension does not pertain to the PCS or MCS SF-36 aggregates. P values come from the Wilcoxon matched-pairs signed rank test; * $P < .05$. Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary; PF, purpura fulminans; SF-36, 36-Item Short-Form Health Survey.

(SD, 0.16; $P = .14$) (Supplementary Table 2). Values obtained in the subscales pertaining to the PCS aggregate displayed no significant differences between exposed and unexposed patients (Figure 2B and Supplementary Table 2). Age-sex standardized values did not differ between exposed and unexposed patients (Supplementary Table 2).

Secondary Outcomes

There was also no significant difference between PF and septic shock survivors regarding the MCS aggregate of the SF-36 questionnaire ($P = .45$; Figure 2A and Supplementary Table 2). Median MCS values were even higher (SD, 0.55) than those of the reference population in exposed patients, but this difference was not larger than that of unexposed patients (SD, 0.37; $P = .75$; Supplementary Table 2). Values obtained in the subscales of the MCS aggregate displayed no significant differences between exposed and unexposed patients (Figure 2B and Supplementary Table 2).

No difference was found between groups regarding median HAD-anxiety and HAD-depression scores, the proportion of patients with a HAD-anxiety score ≥ 8 or HAD-depression score ≥ 5 , median IES-R global score, and the proportion of patients with an IES-R score ≥ 33 , median ADL and IADL scores, and self-assessed quality of life (quantitative score) (Table 2). There was also no difference between groups concerning other general quality of life outcomes (Table 2).

Outcomes in Predefined Subgroups of Interest

As compared to nonamputated PF survivors, PF patients who were amputated exhibited significantly lower SF-36 PCS values (Figure 3A and Supplementary Table 3). Median PCS values of amputated PF survivors were also dramatically lower than those observed in an age-sex standardized population, with a difference >2 SD, while nonamputated survivors did not significantly differ from the reference population (SD, -0.16) (Figure 3A and Supplementary Table 3). Values of the MCS aggregate of the SF-36 questionnaire did not differ between amputated and nonamputated PF survivors. Values obtained in the subscales of the PCS and MCS aggregates of amputated and nonamputated PF patients further depicted dramatic differences between groups, particularly within the PCS subscales (Figure 3B and Supplementary Table 3). Median IADL and quantitative self-assessed global quality of life scores (Table 3) were also lower in amputated patients as compared with their nonamputated counterparts. Yet, no significant difference was observed between amputated and nonamputated patients regarding HAD, IES-R, and ADL scores. As expected, the proportion of patients needing home assistance was higher and that of patients able to walk >500 m was lower in amputated patients compared with others. However, all amputated patients were able to walk, half of them being able to walk >500 m (Table 3) and, remarkably, all amputated patients were living at home at the time the phone interview was performed.

Table 2. Patient-centered Outcomes for Survivors of Purpura Fulminans and Septic Shock

Outcome	Purpura Fulminans (n = 37)	Septic Shock (n = 37)	PValue
Mental health			
HAD-A ^a , median (IQR)	7.0 (4.0–9.0)	7.0 (5.0–9.0)	.82
HAD-A ≥8	16 (43.2)	14 (37.8)	.48
HAD-D ^b , median (IQR)	2.5 (1.0–5.0)	3.0 (2.0–6.0)	.83
HAD-D ≥5	11 (30.6)	16 (43.2)	.41
IES-R ^c , median (IQR)	12 (5–29)	9 (4–18)	.43
IES-R ≥33	6 (16.2)	2 (5.4)	.17
Functioning level/independence			
ADL ^d , median (IQR)	6 (6–6)	6 (5–6)	.59
IADL ^e , median (IQR)	8 (7–8)	7 (7–8)	.92
Self-assessed global quality of life			
Quantitative score ^f , median (IQR)	70 (50–80)	70 (50–80)	.90
General quality of life outcomes			
Current place of residence			.79
Sheltered housing	0	0	
Care home	0	0	
Private home without assistance	31 (83.8)	30 (81.1)	
Private home with assistance	6 (16.2)	7 (18.9)	
Sequelae related to ICU stay	22 (59.5)	9 (24.3)	.008
Amputations	12 (32.4)	1 (2.7)	.019
Scars	8 (21.6)	2 (5.0)	.064
Walking distance			.97
Not able to walk	1 (2.7)	0	
<50 m	1 (2.7)	3 (8.1)	
50–200 m	3 (8.1)	5 (13.5)	
200–500 m	4 (10.8)	1 (2.7)	
>500 m	28 (75.7)	28 (75.7)	
Rehospitalizations	13 (35.1)	20 (54.1)	.020
Current employment status			.15
Full-time employment/studies	18 (48.6)	6 (16.2)	
Part-time employment/studies	4 (10.8)	4 (10.8)	
Occasional employment	0	1 (2.7)	
Unemployed	1 (2.7)	5 (13.5)	
Retired	8 (21.6)	11 (29.7)	
Long-term disability	6 (16.2)	10 (27.0)	
Change in employment status since illness	13 (35.1)	17 (45.9)	.29
Change in family status	5 (13.5)	4 (10.8)	.80
Change in alcohol consumption	1 (2.7)	1 (2.7)	.78
Change in tobacco consumption	3 (8.1)	3 (8.1)	.89
Change in any drug consumption	1 (2.7)	0	>.99
Psychological support			
Proposed	18 (48.6)	17 (45.9)	.66
Requested by the patient	20 (54.1)	19 (51.4)	.22

For each variable, the *P* value was computed using a mixed logistic regression with adjustment for age, Simplified Acute Physiology Score II, and pair as a random effect.

Abbreviations: ADL, activities of daily living; HAD-A, Hospital Anxiety and Depression scale-anxiety; HAD-D, Hospital Anxiety and Depression scale-depression; IADL, instrumental activities of daily living; ICU, intensive care unit; IES-R, Impact of Event Scale-Revised; IQR, interquartile range.

^aThe HAD-A subscale indicates a high probability of anxiety for a value >8.

^bThe HAD-D subscale indicates a high probability of depression for a value >5.

^cIES-R: 22 items scored on a 5-point scale; Complete IES-R score values range from 0 to 88 and a score >33 is the best threshold for a probable diagnosis of posttraumatic stress disorder.

^dADL or Katz's scale (6 items scored 0, 0.5, or 1 [completely independent] for a maximal score value of 6).

^eIADL or Lawton's scale (8 items scored 0, 0.5, or 1 [completely independent] for a maximal score value of 8).

^fAs assessed by the patient on a scale ranging from 0 (worst value) to 100 (best value).

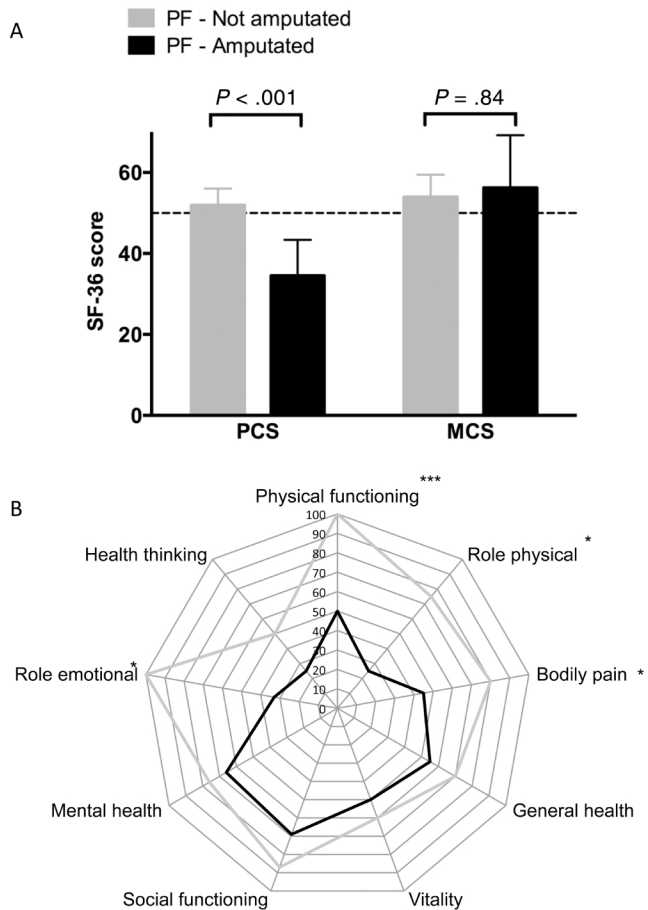


Figure 3. Results of the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) questionnaire in amputated and non-amputated purpura fulminans survivors. *A*, Comparison of the Physical (PCS) and Mental (MCS) component summaries of the SF-36 questionnaire between amputated (black) and non-amputated (gray) patients surviving purpura fulminans (PF). Results are centered on the value of 50 (dashed line; values > or < 50 reflected values higher or lower than age-sex standardized French values). *B*, Comparison of each subdomain of the SF-36 questionnaire between amputated (black) and non-amputated (gray) patients surviving purpura fulminans (PF). The “Physical functioning”, “Role physical”, “Bodily pain”, and “General health” subdimensions pertain to the PCS aggregate component, the “Vitality”, “Social functioning”, “Mental health”, and “Role emotional” subdimensions pertain to the MCS aggregate component, the “Health transition” subdimension does not pertain to the PCS or MCS SF-36 aggregates. *P* values come from the Mann-Whitney test; **P* < .05; ****P* < .001. Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary; PF, purpura fulminans; SF-36, 36-Item Short-Form Health Survey.

Sensitivity Analyses

Patient-centered outcomes were further analyzed in survivors of *N. meningitidis*-related (n = 28) and *S. pneumoniae*-related (n = 8) PF (Supplementary Tables 4–7). Survivors of *N. meningitidis*-related PF showed similar patient-centered outcomes than their septic shock counterparts, except for significantly more sequelae related to ICU stay (57% vs 25%; *P* = .035) and fewer rehospitalizations (29% vs 57%; *P* = .011; Supplementary Table 4). No significant difference was observed regarding median MCS and PCS values, despite significantly higher general health scores in PF compared with septic shock patients

Table 3. Demographics and Patient-centered Outcomes for Survivors of Purpura Fulminans (n = 12) or Did Not Require (n = 25) Amputation

Characteristic	Purpura Fulminans With Amputation (n = 12)	Purpura Fulminans Without Amputation (n = 25)	P Value
Patient characteristics			
Age, y, median (IQR)	47 (28–64)	36 (24–59)	.13
Sex, male/female	3/9	12/13	.29
SAPS II, median (IQR)	61 (42–67)	38 (29–46)	.004
No. of limbs amputated, median (IQR)	4 (1–4)
Requiring prostheses	11 (91.7)		
1 or 2 upper limb(s)	9 (75.0)
1 or 2 lower limb(s)	11 (91.7)
Mental health			
HAD-A ^a , median (IQR)	7.0 (4.5–9.0)	7.0 (4.0–9.5)	.79
HAD-A ≥8	5 (41.7)	11 (44.0)	>.99
HAD-D ^b , median (IQR)	4.0 (2.0–8.0)	1.0 (0.5–5.0)	.12
HAD-D ≥5	4 (36.4)	7 (28.0)	.70
IES-R ^c , median (IQR)	22 (7–36)	11 (4–22)	.10
IES-R ≥33	4 (33.3)	2 (8.0)	.073
Functioning level/independence			
ADL ^d , median (IQR)	6 (5–6)	6 (6–6)	.18
IADL ^e , median (IQR)	7 (4–8)	8 (7–8)	.021
Self-assessed global quality of life			
Quantitative score ^f , median (IQR)	60 (50–70)	80 (70–90)	.006
General quality of life outcomes			
Current place of residence			.009
Sheltered housing	0	0	
Care home	0	0	
Private home without assistance	7 (58.3)	24 (96.0)	
Private home with assistance	5 (41.7)	1 (4.0)	
Sequelae related to ICU stay	12 (100.0)	10 (40.0)	<.0001
Walking distance			.014
Not able to walk	0	1 (4.0)	
<50 m	0	1 (4.0)	
50–200 m	2 (16.7)	1 (4.0)	
200–500 m	4 (33.3)	0	
>500 m	6 (50.0)	22 (88.0)	
Rehospitalizations	6 (50.0)	7 (28.0)	.27
Current employment status			
Full-time employment/studies	2 (16.7)	16 (64.0)	
Part-time employment/studies	2 (16.7)	2 (8.0)	
Occasional employment	0	0	
Unemployed	0	1 (4.0)	
Retired	5 (41.7)	3 (12.0)	
Long-term disability	3 (25.0)	3 (12.0)	
Change in employment status since illness	7 (58.3)	6 (24.0)	.067
Change in family status	0	5 (20.0)	.15
Change in alcohol consumption	0	1 (4.0)	>.99
Change in tobacco consumption	2 (16.7)	1 (4.0)	.24
Change in any drug consumption	1 (8.3)	0	.32
Psychological support			
Proposed	9 (75.0)	9 (36.0)	.069
Requested by the patient	8 (66.7)	12 (48.0)	.32

P values for comparisons of categorical variables come from the Pearson χ^2 or the Fisher exact test and, for comparison of continuous variables, from the Wilcoxon-Mann-Whitney test.

Abbreviations: ADL, activities of daily living; HAD-A, Hospital Anxiety and Depression scale-anxiety; HAD-D, Hospital Anxiety and Depression scale-depression; IADL, instrumental activities of daily living; ICU, intensive care unit; IES-R, Impact of Event Scale-Revised; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II.

^aThe HAD-A subscale indicates a high probability of anxiety for a value >8.

^bThe HAD-D subscale indicates a high probability of depression for a value >5.

^cIES-R: 22 items scored on a 5-point scale; Complete IES-R score values range from 0 to 88 and a score >33 is the best threshold for a probable diagnosis of posttraumatic stress disorder.

^dADL or Katz's scale (6 items scored 0, 0.5, or 1 [completely independent] for a maximal score value of 6).

^eIADL or Lawton's scale (8 items scored 0, 0.5, or 1 [completely independent] for a maximal score value of 8).

^fAs assessed by the patient on a scale ranging from 0 (worst value) to 100 (best value).

(62 [IQR, 45–85] vs 40 [IQR, 20–72]; $P = .037$; Supplementary Table 5). Analysis of survivors of *S. pneumoniae*-related PF, although limited by the small sample size ($n = 8$), did not display significant differences with their septic shock counterparts (Supplementary Tables 6 and 7).

DISCUSSION

We herein report the first multicenter study comparing long-term HR-QOL in patients who survived the acute phase of PF with septic shock controls matched on age, sex, and severity of illness. The main results are as follows: (i) HR-QOL assessed with the SF-36 questionnaire did not significantly differ between patients surviving the acute phase of infectious PF and survivors of septic shock unrelated to PF despite a dramatically higher rate of amputation in the former group as compared with the latter; (ii) among PF survivors, those who required limb amputation had a significantly impaired HR-QOL with lower PCS of the SF-36 questionnaire compared to those who did not require limb amputation.

Several studies have shown that HR-QOL is impaired in patients surviving sepsis, as compared with the general population [24–28]. In the subgroup of adult patients surviving a septic shock related to PF, data on long-term HR-QOL are scarce. Only one small uncontrolled study [29], involving 17 college students surviving the acute phase of meningococcal disease (including acute meningitis and PF), showed a satisfying HR-QOL when using the EuroQol quality of life score [30]. To the best of our knowledge, our report is the first controlled study investigating long-term HR-QOL in adult patients surviving infectious PF. Patients surviving PF are usually young and previously healthy [2, 3], implying good physical recovery, potentially minimizing long-term HR-QOL impairment. However, almost one-third of patients surviving the acute phase of PF needed limb amputations, with a median number of 4 amputated limbs in the current cohort, potentially leading to severe disability and impaired HR-QOL. In this context, the assessment of HR-QOL is particularly relevant.

Thirty-seven patients, who were well representative of the survivors of our large PF cohort [1], with similar age, SAPS II, sex ratio, and proportion of amputated patients, were eventually phone-interviewed by 2 ICU nurses who were blinded to the PF-exposed/unexposed status. Strikingly, PF survivors exhibited similar HR-QOL than septic shock survivors. The relatively young age of our patients (43 years old in exposed patients and 53 years old in unexposed patients) and the absence of previous comorbidity in almost three-quarters of exposed patients may account for this apparently satisfactory long-term recovery. Yet, although the PCS of PF survivors was not significantly lower than that of septic shock survivors after adjusting for age and SAPS II, it was >0.5 SD lower than the reference population, indicating a substantial impairment in the physical dimensions of HR-QOL; Such finding is consistent with the fact that almost 60% of PF survivors declared

having sequelae related to ICU stay, mainly including amputations and scars, as compared to 24% of septic shock survivors.

Among PF survivors, those who required limb amputations exhibited significantly poorer HR-QOL when compared with nonamputated patients, with nonsurprisingly lower PCS and IADL scores. Importantly, these physical sequelae were quantified 55 months after ICU discharge, suggesting patients had reached a steady state of disability. However, some aspects pertaining to the HR-QOL of PF survivors, amputated or not, certainly deserve to be underlined: (i) Despite the high proportion of patients with lower limb amputation (92%), more than half of them lived at home without assistance and were able to walk >500 m; (ii) Scores measuring the mental health of amputated vs nonamputated patients were relatively preserved with a similar proportion of patients displaying symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD), consistent with the well-described resilience phenomenon [31].

One of the strengths of our study is the relatively large number of included patients despite the very low incidence of PF, its multicenter design, the prolonged delay between ICU discharge and phone interviews, and the comparison of HR-QOL with a controlled group, which we attempted to match on age, sex ratio, and severity score. Yet, PF patients were systematically younger than their counterparts resulting in a trend toward a lower age, and had nonstatistically higher SAPS II scores. We accounted for these imbalances by performing a mixed logistic regression with adjustment for age, SAPS II, and pair as a random effect. SF-36 values were also standardized for age and sex. Unexposed patients also had a higher proportion of neoplastic diseases, diabetes mellitus, and obesity; however, accounting for these comorbidities was not possible as most exposed patients had no comorbidity. We also acknowledge that, because of the extended delay between ICU admission and phone interview, half of the patients were lost to follow-up. However, these patients had similar characteristics than phone-interviewed patients, thus limiting the risk of selection bias.

We also used numerous validated psychological instrument scales to explore both physical and mental components of HR-QOL, including the SF-36, which is recommended as the most appropriate instrument to be used in critical care long-term outcome studies [27, 32–34]. Because of the design of the study, we were not able to assess HR-QOL before ICU admission, and exposed and unexposed patients were not matched for before-ICU HR-QOL, which may be determinant for assessing after-ICU HR-QOL. Moreover, we cannot exclude that the absence of statistical difference measured between PF and septic shock patients regarding PCS and between amputated and nonamputated PF survivors regarding PTSD risk assessment was merely due to a lack of power inherent to the limited number of patients included. The absence of difference in long-term HR-QOL between patients surviving the acute phase of an infectious PF and those surviving a septic shock unrelated to PF should encourage intensivists to provide an early and aggressive treatment of

patients with PF. In patients with distal limb necrosis, the decision to perform disabling limb amputations is a crucial ethical issue. Indeed, limb amputations seem to significantly impair HR-QOL, and the decision to perform disabling limb amputations should be cautiously considered on a case-by-case basis and involve a multidisciplinary team (intensivists, surgeons, physiotherapists, nurses, psychologists). However, the decision of limb amputation is often decided after the acute phase of PF, when the patients have fully recovered from septic shock. To minimize the impact of such limb amputations on HR-QOL, those patients who require limb amputations should benefit from a long-term multidisciplinary follow-up including functional therapist, physiotherapist, ergotherapist, psychologist, and psychiatrist, as soon as possible after ICU discharge.

In conclusion, long-term HR-QOL did not significantly differ between patients surviving PF and those surviving septic shock unrelated to PF of similar age, sex, and severity of disease. Among PF survivors, those who required limb amputation had an impaired long-term physical HR-QOL but seem to have a preserved mental health.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. D. R. has received personal fees from Astellas. S. J. reports consulting fees from Drager, Hamilton, Maquet, and Fischer and Paykel, outside the submitted work. S. E. has received personal fees from Aerogen, La Diffusion Technique Française, and Baxter, and grants from Aerogen, Fisher and Paykel, and Hamilton Medical. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

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