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Risk Factors and Outcome Associated With Fungal Infections in Patients With Severe Burn Injury: 10-year Retrospective IFI-BURN Study

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Background. In burn patients, skin barrier disruption and immune dysfunctions increase susceptibility to invasive fungal diseases (IFDs) like invasive candidiasis (IC) and invasive mold infections (IMI). We provide an in-depth analysis of IFD-related factors and outcomes in a 10-year cohort of severe burn patients.

Methods. This retrospective cohort study includes adult patients admitted to the burn intensive care unit (BICU) between April 2014 and May 2023 with total burn surface area (TBSA) ≥15%. Patients were classified as proven IFD according to EORTC/MSGERC criteria applicable for IC. Putative IMIs were defined with: ≥2 positive cultures from a skin biopsy/bronchoalveolar lavage or ≥2 positive blood specific-quantitative polymerase chain reactions (qPCRs) or a combination of both.

Results. Among 1381 patients admitted, 276 consecutive patients with TBSA ≥15% were included. Eighty-seven (31.5%; IC n = 30; IMI n = 43; both n = 14) patients fulfilled the criteria for probable/putative IFD. At Day 30 after the burn injury, the estimated cumulative incidence proven/putative (pr/pu) IFD was 26.4% (95% confidence interval [CI], 21.4%–31.8%). Factors independently associated with IFDs were TBSA, severity scores and indoor burn injury (ie, from confined space fire). Overall mortality was 15.3% and 36.8% in the no IFD, pr/pu IFD groups respectively ($P < .0001$). IFD was independently associated with a risk of death (hazard ratio [HR]: 1.94 for pr/pu IFD; 95% CI, 1.12–3.36; $P = .019$).

Conclusions. This study describes twenty-first-century characteristics of IFDs in severe burn patients confirming known risk factors with thresholds and identifying the indoor injury as an independent factor associated to IFDs. This suggests a link to contamination caused by fire damage, which is highly susceptible to aerosolizing spores.

Keywords. invasive fungal disease; burn wound; critical care; risk factors; outcome.

Despite important advances in the care of critically ill burn patients, infectious complications remain one of the leading causes of morbidity and mortality [1]. Sepsis, caused primarily by bacterial and fungal infections, is a daily ongoing diagnostic challenge in this population [2]. Common risk factors associated with invasive fungal diseases (IFDs) in the intensive care unit (eg, catheters, broad-spectrum antibiotics), combined with skin barrier disruption and immune dysregulation in burn patients, make this population particularly susceptible to fungal superinfection. Two types of IFDs are seen in burn patients. (i) Invasive candidiasis most commonly present as candidemia originating from translocation of intestinal or skin flora due to increased intestinal permeability (eg, acute mesenteric ischemia) or damaged skin barrier (*ie,* burned skin, catheters). (ii) Invasive mold infections (IMIs) are caused by mycelial growth from ubiquitous spores of saprophytic fungi (ie, *Aspergillus* spp., Mucorales, *Fusarium* spp.) at the expense of burned skin or damaged airways after smoke inhalation.

In the light of a changing standard of care [3, 4], new diagnostic options including molecular biology tools [5], and a broader antifungal arsenal, an updated view of IFDs in this population is needed to identify contemporary issues and gaps to improve the management of critically ill burn patients. Here we provide an in-depth analysis of the risk factors associated with IFDs and the resulting outcomes in a 10-year cohort of patients with severe burns.

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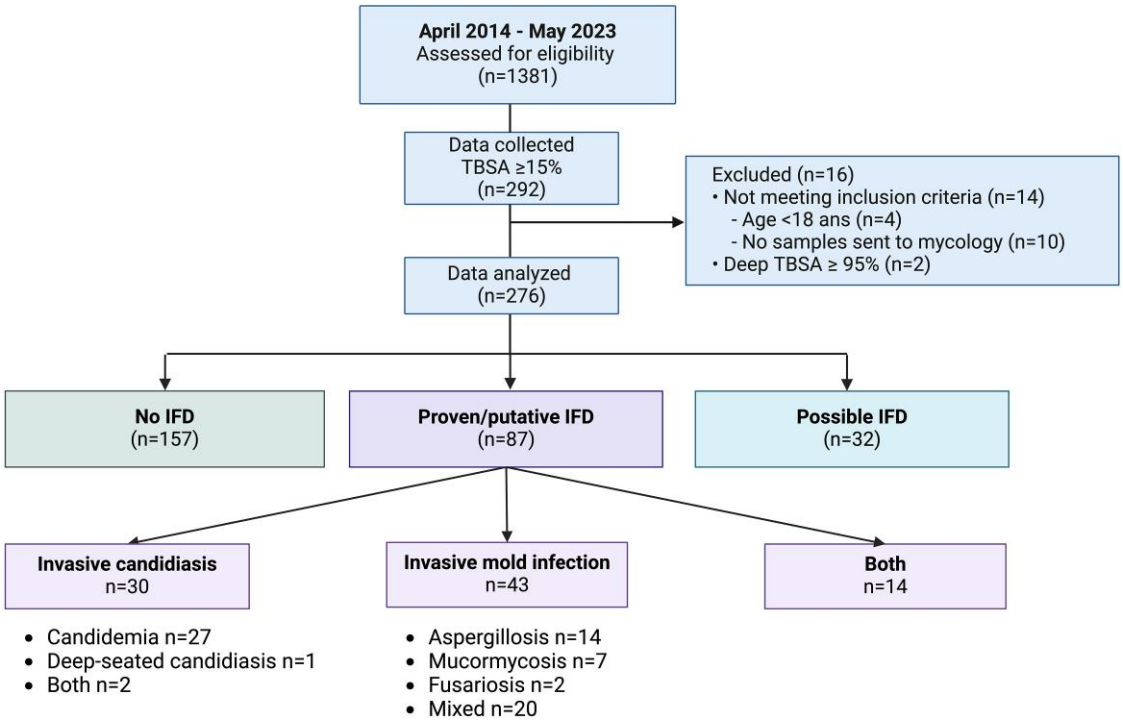

Figure 1. Flow chart of the study. Abbreviations: IFD, invasive fungal disease; TBSA, total burn surface area. Created with BioRender.com.

METHODS

Patients and Study Design

We retrospectively analyzed all consecutive patients admitted to our burn intensive care unit (BICU) between April 2014 and May 2023 with a total burn surface area (TBSA) ≥15% and the samples sent to the mycology department were included (Figure 1). Deep partial thickness definition according to Jeschke et al was used to define deep burn surface area (DBSA) [1]. Demographic and clinical data, including comorbidities, burn injury characteristics, clinical severity score (sequential organ failure assessment [SOFA] [6], Simplified acute physiology score [SAPS] II [7], abbreviated burn severity index [ABSI] [8]), laboratory data, antifungal treatments, length of BICU stay, and mortality were recorded in the electronic case report form. Inhalation injury was diagnosed by bronchoscopy according to Endorf et al [9]. Initial hemodynamic management was guided by our previously published protocol [10]. Aerobiocontamination was limited by (i) air purifiers (ii) an air handling unit (iii) chamber overpressure [11], but spore load in the environment is not routinely assessed. To note, 15 patients were previously included in a multicentric cohort studying outcome [12].

Patients were classified as proven IFD according to European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSG) consensus criteria applicable for candidemia and deep-seated candidiasis [5]. Although burns are a known risk factor for IMIs, they are not listed as a host factor. Also, we proposed the following case definition for putative IMI: severe burn injury with worsening despite appropriate standard of care and the following mycological criteria: ≥2 positive culture from skin biopsy/bronchoalveolar lavage (BAL) or ≥2 positive blood specific quantitative polymerase chain reaction (qPCR) or ≥1 positive culture and ≥1 positive qPCR due to the same fungal genera. Patients with only 1 positive mycological criterion out of several were considered as possible IFD. Appropriate antifungal management for candidemia and IMI was considered a combination of antifungal treatment and catheter removal or surgical debridement respectively. No empirical therapy was prescribed (Supplementary Figure 1).

Mycology Criteria Testing

Mycological data were recorded from blood culture, BAL, skin biopsy, and peritoneal lavage. Handling of samples is detailed in Supplementary Table 1. We define a new candidemia or bacteremia episode as occurring 14 days after a distinct microorganism was identified. Specific qPCR (*Aspergillus fumigatus*, Mucorales, *Fusarium*) have been performed in plasma, tissue, and BAL [13–15]. To note, after 2016 a weekly screening strategy with weekly plasma *Aspergillus fumigatus* and Mucorales qPCR was implemented [16].

Statistics

Summary statistics were computed, namely, median (with interquartile range [IQR]) for quantitative variables and percentage for qualitative ones. Time to IFD was computed from the date of burn, in a competing risk setting due to prior deaths; occurrence of possible IFD was be distinguished from the proven/putative (pr/pu) events, separately. Pr/pu IFD were also segregated according to the origin of infection (candidiasis, mold, both). Comparison of cumulative incidence across independent baseline groups were based on the Gray test [17]. To look further for risk factors of IFD, we considered the cause-specific hazard of IFD, modeled through univariate and multivariate Cox models. Overall survival was computed after burn, then after IFD, using the Kaplan-Meier method, with comparisons across baseline groups defined at burn and at IFD diagnosis respectively, based on the Cox models, with estimated hazard ratio (HR) of death. Landmark analyses were also performed selecting patients alive at day 12. Finally, to assess whether the occurrence of IFI over time may have impacted the occurrence of death, we computed survival after burn according to the time-dependent IFD status, that prohibited the use of the standard methods due to immortal bias. Thus, we used the Simon and Makuch survival estimator [18] and a time-dependent Cox model. All analyses were performed using R 4.1.1 (http://www.r-project.org).

Ethical Statements

Our institutional ethics committee approved the study (IDRCB, IRB00003835; 2013/17NICB). Written information was given to the patient or the next of kin.

RESULTS

Patients' Characteristics

Between April 2014 and May 2023, 1381 patients with severe burn injuries were admitted to Saint-Louis tertiary hospital BICU. A total of 282 patients with ≥15% total burn surface area (TBSA) were enrolled in the IFI-BURN study. Also, 4 patients and 2 patients were further excluded due to protocol deviations and deep burn surface area (DBSA) ≥95%, respectively (Figure 1). The remaining 276 patients were included in the further analyses.

Median age was 47.5 [IQR: 34; 61] years, and 175 (63.4%) patients were men. Median body mass index (BMI) was 25.4 [IQR: 23.1; 29.3] kg/m^2. Baseline characteristics and comorbidities for all patients and among IFD groups are shown in Table 1. Most frequent comorbidities were psychiatric disorder (33.0%), hypertension (23.4%), alcoholism (21.9%), and diabetes (11.4%). Only one patient was immunocompromised prior to burn injury (ie, chemotherapy for cancer) and did not develop IFD. Origin of burn injury was mostly thermal (97.1%), and median TBSA and DBSA were 33 [IQR: 25; 50] % and 20 [IQR: 6; 36] %, respectively. All patients had a central venous catheter.

Median length of stay in the ICU was 42 [IQR: 26; 67] days. During the ICU stay, 87 (31.5%) patients fulfilled criteria of proven/putative (pr/pu) IFD (ie, 6.3% (87/1381) of total admitted patients), 32 (11.6%) those of possible invasive mold infection. A total of 59 (21.4%) patients died after burn (51 within the first 90 days and 8 thereafter [94 to 244 days]). Among them, 35 (59.3%) died after a IFD diagnosis, and 24 (40.7%) died with all mycological testing negative (Supplementary Figure 2).

Mycological Description of IFDs

Among the 87 (31.5%) pr/pu, 44 (15.9%) developed invasive candidiasis (candidemia, n = 39; peritonitis, n = 5) and 57 (20.7%) developed putative invasive mold infection (IMI). To note, 14 (5.0%) patients had both. Mold infections were due to *Aspergillus* sp. (n = 42), Mucorales (n = 26) and *Fusarium* sp. (n = 23) frequently found in association (n = 26; 45.6% of patients with IMI). Among putative IMIs, we identified 49 soft tissue infections, 8 pulmonary infections and 8 cases where the point of origin could not be clearly determined (repeated blood qPCR only). All species responsible for pr/pu IFDs are shown in Supplementary Figure 3. Aside from fungal infections, 220 patients (79.7%) were diagnosed with at least 1 episode of bacteremia. The cumulative incidence of IFD, according to the diagnostic group, as well as that of death prior to any IFD are displayed in Figure 2. At day 30 after burn injury, the estimated cumulative incidence proven or putative IFD was 26.4% (95% confidence interval [CI], 21.4%–31.8%). Pr/pu IFDs were diagnosed at a median of 12 [IQR: 8; 22] days after burn injury, earlier for IMD (10 [IQR: 5; 17] days) than invasive candidiasis (17 [IQR: 11; 30] days) ($P = .001$). A proportion of 91.1% of patients with IFDs received targeted antifungal molecules, and 80.5% received full appropriate antifungal management. Among patients who did not (n = 17), mortality rate was not statistically different from the others (35.5% vs 37.1%; $P = .88$).

Factors Associated With IFDs

Based on univariate analyses (Supplementary Table 2), there were no significant impact of demographic characteristics and comorbidities on the risk of IFD, beside that of age ($P = .036$). The following burn and baseline characteristics were associated with the occurrence of IFD: circumstances of burn injury (indoor (ie, from confined space fire) ($P = .039$, Figure 3*A*) and smoke inhalation ($P < .0001$), Figure 3*B*), increased TBSA (Figure 3*C*) and DBSA ($P < .0001$) (Figure 3*D*) and increased severity scores at admission ($P < .0001$) (Supplementary Figure 4). A multivariate model was fitted to the 262 complete cases. Based on Akaike criterion, indoor burn, DBSA, SOFA score, and ABSI were considered to add to each other prognostic information (Table 2).

Table 1. Demographic and Baseline Characteristics and Clinical Course Data Among Invasive Fungal Disease Groups

	All Patients (n = 276)	No IFD (n = 157)	Proven And Putative IFD (n = 87)	Possible IFD (n = 32)
Demographic characteristics				
Sex female, n (%)	101 (36.6%)	52 (33.1%)	35 (40.2%)	14 (43.8%)
Age median [IQR]	48 [34: 61]	44 [31; 62]	51 [40; 64]	50 [35; 55]
BMI median [IQR]	25.4 [23.1; 29.3]	25.7 [23.5; 29.7]	26 [22.9; 29.4]	24.4 [22.8; 27.6]
Comorbidities, n (%)				
Alcohol, n (%)	60 (21.9%)	31 (19.8%)	21 (24.4%)	8 (25.8%)
Psychiatric disease	90 (33.0%)	48 (30.8%)	32 (37.2%)	10 (32.3%)
Diabetes	31 (11.4%)	18 (11.5%)	9 (10.5%)	4 (12.9%)
Hypertension	64 (23.4%)	38 (24.4%)	20 (23.4%)	6 (19.4%)
Cardiovascular disease[a]	20 (7.3%)	13 (8.3%)	4 (4.6%)	3 (9.3%)
Pulmonary disease[b]	10 (3.7%)	8 (5.1%)	0 (0%)	2 (6.3%)
Immunocompromised	1 (0.4%)	1 (0.6%)	0 (0%)	0 (0%)
Cirrhosis	5 (1.8%)	3 (1.9%)	1 (1.2%)	1 (3.2%)
Hypothyroidism	10 (3.7%)	2 (1.3%)	7 (8.1%)	1 (3.2%)
Cancer	15 (5.5%)	11 (7.1%)	3 (3.5%)	1 (3.2%)
Baseline characteristics				
Type of burn injury				
Thermal	268 (97.1%)	151 (96.2%)	86 (98.9%)	31 (96.9%)
Electric	9 (3.3%)	7 (4.5%)	1 (1.2%)	1 (3.1%)
Chemical	2 (0.7%)	2 (1.3%)	0 (0%)	0 (0%)
Smoke inhalation	103 (37.6%)	42 (26.8%)	46 (53.5%)	15 (48.4%)
Indoor injury	201 (74.4%)	106 (68.8%)	70 (80.5%)	25 (86.2%)
TBSA median [IQR]	33 [25; 50]	28 [20; 39]	45 [32; 68]	35 [20; 52]
DBSA median [IQR]	20 [6; 36]	12 [5; 25]	30 [20; 56]	18 [5; 35]
Severity score at admission				
ABSI median [IQR]	8 [6; 10]	7 [6; 9]	10 [8.5; 12]	8 [7; 9.3]
SAPSII median [IQR]	30 [20; 43]	25 [17; 36]	36 [29; 49]	29 [22.3; 44.8]
SOFA median [IQR]	4 [1; 8]	3 [0; 6]	7 [4; 9]	6.5 [3.3; 8]
Clinical course data				
Surgery n (%)	125 (45.5%)	52 (33.3%)	59 (67.8%)	14 (43.8%)
Delay post-burn (d)	0 [0; 1]	0 [0; 0]	0 [0; 0.5]	1 [0; 1]
Total surgery median [IQR]	6 [4; 8]	5 [3.3; 6]	8 [6; 11]	5 [4.3; 6]
Intravenous fluids (mL) H24	12 000 [7000; 17 000]	9755 [5575; 14 520]	16 000 [12 000; 21 800]	12 000 [8000; 16 700]
Length mechanical ventilation (d)	16 [7.3; 34.8]	9 [3; 18]	37 [17; 64]	13.5 [6; 25.3]
Renal replacement therapy, n (%)	48 (17.4%)	11 (7.0%)	34 (39.1%)	3 (9.4%)
Bacteremia, n (%)	220 (80.0%)	108 (68.8%)	85 (97.7%)	27 (84.4%)
Death, n (%)	59 (21.4%)	24 (15.3%)	32 (36.8%)	3 (9.4%)
LOS ICU (d) [IQR]	42 [26; 67.3]	32 [21; 45]	74 [42; 96]	51 [33; 69]
Sequelae at 1 y n/followed (%)	70/85 (82.4%)	25/32 (78.1%)	30/36 (83.3%)	15/17 (88.3%)
Returned to work n/followed (%)	24/66 (36.4%)	11/22 (50%)	6/31 (19.4%)	7/13 (53.9%)

Abbreviations: DBSA, deep burn surface area; IFD, invasive fungal disease; IQR, interquartile range; LOS ICU, length of stay in the intensive care unit; NP, not performed (small sample); TBSA, total burn surface area.

[a]Cardiovascular diseases: ischemic cardiopathy, chronic heart failure or stroke.

[b]Pulmonary disease: chronic lung failure, chronic obstructive pulmonary disorder.

Among the 87 pr/pu IFDs, baseline characteristics and outcome were compared according to the type of IFD (ie, invasive candidiasis [IC] or invasive mold infection [IMI]). Significant differences were observed for pre-existing diabetes more prevalent among patients who developed IC (23.3% vs 4.7%; $P = .02$). Older age was observed in patients who developed IC (58 [IQR: 47–69] vs 47 [IQR: 36–61] but not significantly ($P = .059$]) (Supplementary Table 3). In a multivariate Cox models factors associated with IC were age and ABSI, whereas factors associated with IMI was age, DBSA, and SOFA score (Supplementary Table 4).

Impact of IFDs on Outcomes

Overall mortality was 15.3%, 36.8%, and 9.4% in no IFD, pr/pu IFD, and possible IFD groups, respectively ($P < .0001$). Similarly, length of stay in the BICU was 32 [IQR: 21; 45], 74 [IQR: 42; 96] and 51 [IQR: 33; 69] ($P < .0001$) (Table 1). The occurrence of IFD over time impacted the occurrence of death with a significant increase of the hazard of death after pr/pu IFD diagnosis (HR: 1.94; 95% CI: 1.12–3.36; $P = .019$), whereas the occurrence of possible IFD did not significantly impact the outcome (HR: 0.57; 95% CI: .17–1.89; $P = .36$) (Figure 4). Furthermore, a landmark analysis at day 12 (ie, median onset

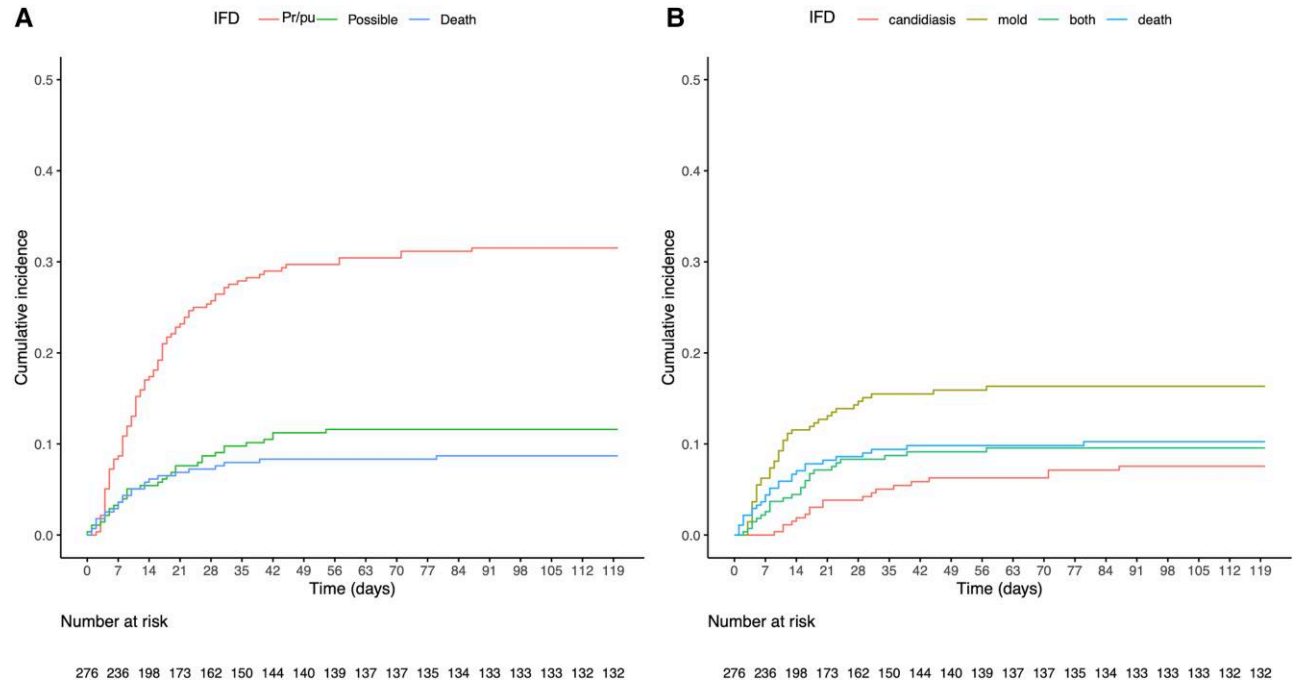

Figure 2. Cumulative incidence of IFD and competing deaths after burn. *A*, Distinction between proven/putative and possible IFD or *B*, proven/putative invasive candidiasis and mold disease. Abbreviation: IFD, invasive fungal disease.

of IFDs) showed an overlap of survival curves between no IFDs and possible IFDs group (Supplementary Figure 5). The predictive factors of death within 30 days after proven/putative IFD were assessed using univariate Cox model. At the 10% level, old age ($P = .048$), high BMI ($P = .004$), TBSA, DBSA, and ABSI score were associated with the risk of death (Table 3). A multivariable model showed that age, BMI, and DBSA added to each other prognosis information (Supplementary Table 5). Overall mortality and length of stay was not significantly different according to the type of IFD although higher in IC (43.3%) than in IMI (27.9%) ($P = .17$).

DISCUSSION

Severe burn injury is a well-known risk factor for IFDs [19]. However, within this population very few studies have systematically studied these infections. To our knowledge, this is the largest cohort study investigating risk factors associated with IFDs due to both filamentous fungi and yeasts in patients with severe burn injury. Among this homogenous population of 276 adult patients with TBSA ≥15%, we recorded 87 pr/pu IFDs according to EORTC/MSGERC criteria for candidemia and our case definition for IMI. Patients represents in total 6.3% of total patients admitted to our burn center. Becker et al in the 1980s and Horvath et al in the 1990s, both over a 10-year experience study based on histologic identification of hyphae in the tissue, found a 9.9% (209/2114) and 2.0% (54/2651) incidence of IFD, respectively [20, 21]. Two multicentric studies with various diagnostic algorithm (ie, ≥1 fungal culture from any site for the first, a complex algorithm with type of sample and pr/pu/colonization variable for the second) found an incidence of 6.29% (435/6918) and 1.1% (94/8503), respectively [12, 22]. Various factors could impact incidence of IFDs in our cohort. Underestimating factors are the 1105 patients with <15% TBSA not reviewed and the 10 patients with ≥15% TBSA but without samples sent to mycology. Factors that can increase incidence compared to older studies is the improvement of mycological diagnosis techniques including molecular tests, weekly screening for circulating DNA of molds in our case [16]. Indeed, 13.0% (9/69) of patients with IMI were diagnosed on ≥2 positive molecular tests only. Four patients considered as possible IMI only had only 1 positive Mucorales qPCR and 2 (50%) received a course of amphotericin B and survived.

The incidence of IFD is confirmed to be primarily linked to TBSA and severity scores, such as ABSI (a colinear variable including TBSA) and SOFA, with the newly identified correlation with indoor burn injury. Our findings further support the notion that the hazard ratio approximately exceeds 1 when TBSA ≥40%, DBSA ≥20%, SAPSII ≥30 and SOFA ≥4 indicating these thresholds as critical points associated with an increased risk of IFD. It is noteworthy that TBSA, ABSI, and SOFA, however, exhibit colinearity and recognizing this interdependence is necessary for a nuanced understanding of IFD

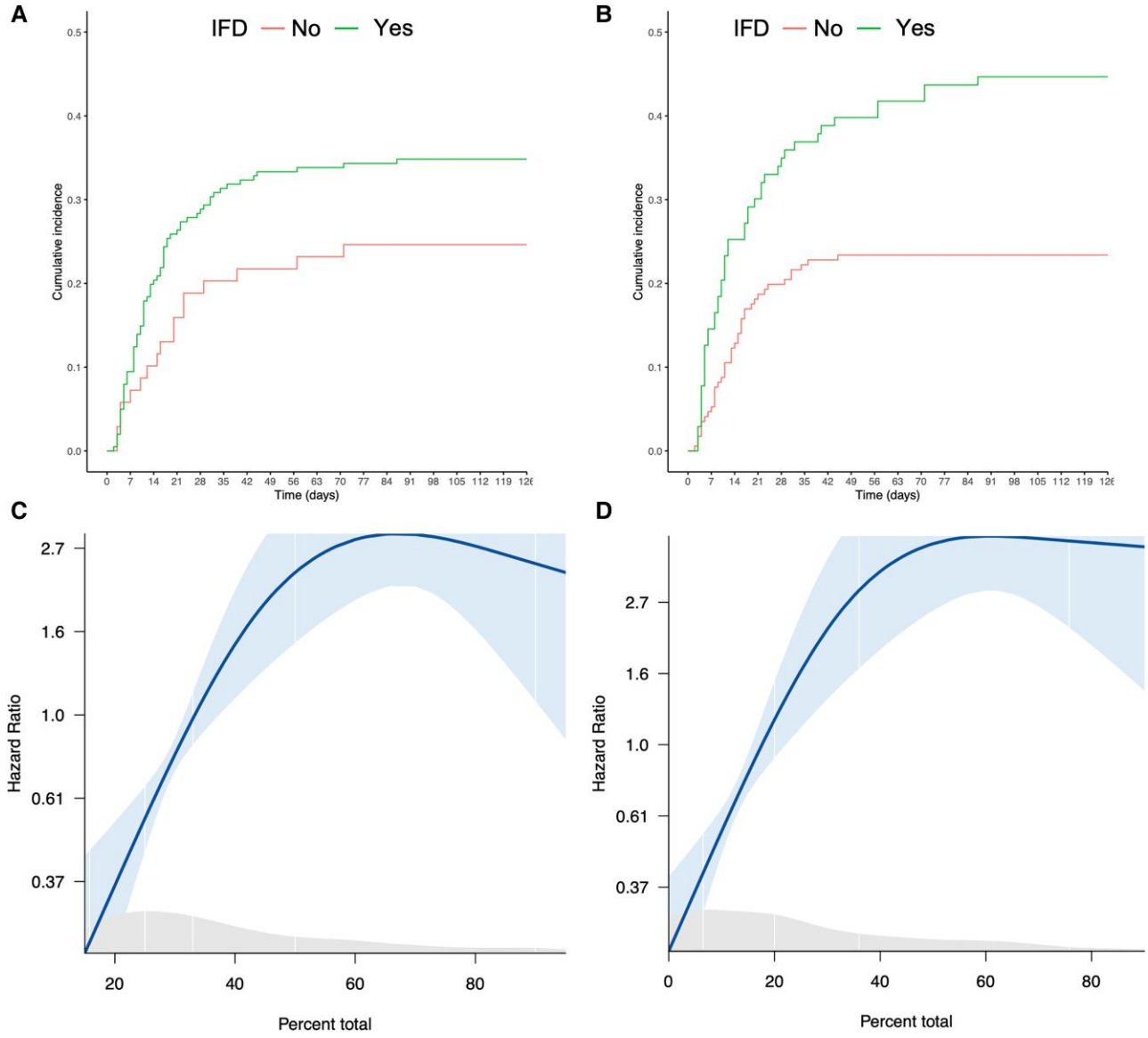

Figure 3. Risk factors of proven/putative (pr/pu) IFDs. Cumulative incidence of pr/pu IFD according (*A*) to closed environment and (*B*) smoke inhalation. Influence of (*C*) total and (*D*) deep surfaces of burn on the cause-specific hazard of pr/pu IFD. Confidence interval is represented by the blue zone. Distribution of patients is represented by the gray zone. Abbreviation: IFD, invasive fungal disease.

risk factors. Indoor burn injury has not previously been reported as a risk factor but was found here to be associated with IFDs especially due to molds. Viable spore concentration is increased indoors compared with outdoors and may further be aerosolized due to fire damage to the building suggesting a contamination that originates at the time of the burn injury [23]. This could also be linked to higher inhalation injury although identified only in the univariate model. Diabetes correlated with candidiasis ($P = .012$) but not IMI ($P = .17$). The occurrence of bacteremia, implying antibiotic prescription, was associated with the occurrence of IFDs ($P < .0001$). Hyperglycemia affects wound healing and immunity and was previously shown to increase the risk of candidemia [24, 25]. Diabetes is a well-known risk factor for rhino-orbito-cerebral mucormycosis but was not associated to IMI in our cohort. Unexplored risk factors are most likely specific immune dysregulation. In severe burn injury, many immune functions are severely compromised, including neutrophil oxidative burst capacity, phagocytosis and neutrophil extracellular trap (NET) generation, which are essential in antifungal immunity [26]. Impaired humoral immunity may also play a role that we plan to explore in serum of patients from this cohort to identify immune profile of at-risk patients.

Observed mortality in our cohort was 15.3%, 9.4%, and 36.8% in no IFD, possible IFD, and pr/pu IFD groups, respectively. The higher mortality rate in no IFD compared to

Table 2. Multivariate Cox Models of Proven/Putative Invasive Fungal Diseases (IFDs) Only and all IFDs After Akaike Criterion Selection

	Pr/pu IFDs		All IFDs	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.094 (.969–1.234)	.15	-	-
Indoor burn injury	1.638 (.941–2.849)	.081	1.895 (1.154–3.111)	**.012**
DBSA	1.217 (1.063–1.393)	**.004**	1.142 (1.015–1.284)	**.027**
SOFA	1.228 (1.079–1.397)	**.002**	1.237 (1.105–1.385)	**.0002**
ABSI	3.825 (1.258–11.6)	**.018**	3.259 (1.225–8.670)	**.018**

To note, criteria included before the Akaike criterion selection were age, inhalation, indoor burn, TBSA, DBSA, SAPSII, SOFA and ABSI. Bold values highlight *P* values <0.05

Abbreviations: ABSI, abbreviated burn severity index; CI, confidence intervals; DBSA, deep burn surface area; HR, hazard ratio; IFD, invasive fungal disease; Pr/pu, proven/putative; SOFA, sepsis-related organ failure assessment.

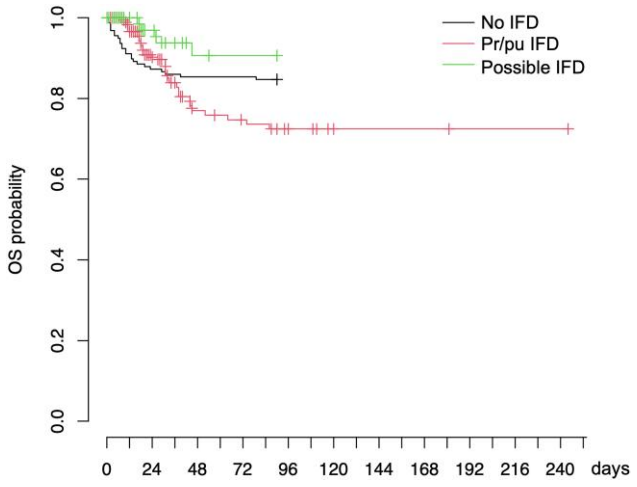

Figure 4. Influence of the occurrence of IFD over time in overall survival. Simon and Makuch survival plots. Abbreviations: IFD, invasive fungal disease; Pr/pu, proven and putative.

possible IFD can be explained by survival bias of less severe cases supported by the overlap of survival curves in the landmark analysis at the median onset delay of IFDs (ie, day 12) (Supplementary Figure 5). The older large cohort found 5.3%, 27.3%, and 75.9% mortality in no IFD criteria, colonized and infected patients, respectively [21]. Yet comparison is difficult considering that TBSA was higher in their infected group than in our pr/pu IFD group (64 [49; 76] % vs 45 [32; 68] %) and our no IFD group includes only patients with ≥15% TBSA [21]. Although a more recent study finds higher mortality in IMIs than candidemia (ie, 52.0% vs 31.9%) [12], we observe the opposite (27.9 vs 43.3%) [27]. Improved prognosis could be due to systematic screening for mucormycosis associated with early treatment strategy since 2016 in our center [16]. The implementation of this strategy decreased mortality rate

Table 3. Prognostic Value of Patients' Characteristics Using Mortality at Day 30 After Proven/Putative Invasive Fungal Disease Diagnosis as Main Outcome

Parameters	HR (95% CI)	*P* Value
Demographic characteristics		
Age	1.24 (1–1.54)	**.048**
Sex (female)	1.31 (.65–2.63)	.45
BMI	1.1 (1.03–1.17)	**.004**
Comorbidities		
Alcohol	1.27 (.59–2.75)	.54
Psychiatric disease	0.88 (.42–1.82)	.73
Diabetes	0.98 (.3–3.23)	.98
Hypertension	1.97 (.93–4.16)	.076
Baseline characteristics		
Smoke inhalation	2.00 (.94–4.25)	.071
Indoor burn injury	1.06 (.44–2.58)	.89
TBSA	1.02 (1–1.03)	**.029**
DBSA	1.02 (1–1.03)	**.012**
ABSI	1.15 (1.01–1.31)	**.039**
IGS2	1 (.99–1.02)	.66
SOFA	1.04 (.94–1.15)	.45

Bold values highlight *P* values <0.05. Abbreviations: ABSI, abbreviated burn severity index; BMI, body mass index; DBSA, deep burn surface area; HR, hazard ratio; Pr/pu: proven/putative; SOFA, sepsis-related organ failure assessment; TBSA, total burn surface area.

from 80% to 33% [16]. We overall identified the same predictive factors (eg, age, TBSA, DBSA, severity scores) with the addition of higher BMI than previous studies [12, 21]. Increased length of stay was reported in burn patients with candidemia [25] but not for IMIs, which in our case was higher than for candidemia, although not significant (Supplementary Table 3). This could, however, reflect patient's severity and increased exposure to the risk of developing IFD. A multivariable model to study the impact of IFD on patient survival after adjusting to baseline characteristics was not performed because of time-varying confounders that could not be taking into account.

The major limit of this work is the difficulty to precisely compare our results with other studies due to the lack of consensual case definition for IMIs in patients with severe burn injury. Moreover, the considerable prevalence of mixed mold infections, also described in cases of invasive pulmonary mold infections and most likely underdiagnosed [28, 29], warrants further investigation and discussion. Our study is unable to determine whether only specific mold species are responsible, although others merely colonize the affected area, or if a synergistic interaction contributes to the degradation of soft tissues. Clinical classification and description of burn wound infections are non-specific based on bacterial infections, whereas mold infections are mostly responsible for non-specific necrosis at early stage and may take on a moldy appearance in the absence of appropriate treatment [19]. Proven IFDs should rely accordingly with EORTC/MSGERC criteria on the histopathological evidence of hyphae in tissue associated with tissue damage [5].

However, skin biopsies are not sterile samples, and burn-associated damages may lead to challenging interpretation. Furthermore, the time for histopathologic processing may delay diagnosis and initiation of antifungal therapy. Therefore, putative diagnosis criteria are needed. The latest EORTC/MSGERC criteria now include molecular biology tools especially when repeatedly positive or associated to other mycological criteria. Circulating fungal DNA in blood is a surrogate for angio-invasive infection and two positive samples remove the doubt regarding false positivity and transitory incidental fungal DNA circulation. Our criteria proposition (ie, ≥2 positive skin biopsy cultures or ≥2 blood qPCRs or ≥1 culture and ≥1 qPCR) seems to adequately predict IFDs considering that patients who did not meet these criteria, defined as possible IFDs, had similar prognosis characteristics than the no IFD group, whereas only 12.5% (4/32) received adequate antifungal therapy for ≥7 days.

Overall, this is a major cohort to appraise characteristics of IFDs in patients with severe burn injury in the twenty-first century. We used a pragmatic definition for putative IFD aligned on the most recent EORTC/MSGERC criteria and identify current risk factors and outcome determinants. Whether fungal infection itself contributes causally to mortality or just represents a marker for other contributors remains difficult to identify. Combining clinical risk factors and immune markers could identify most at-risk patients who could benefit from antifungal prophylaxis. Future studies should identify the part played by the immune system and the microbiome to propose a new model and strategy to further improve therapeutic management of critically ill burn patients.

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

Author Contributions. S. D., E. D., A. A., B. D., and F. D. designed the study; S. T. and E. D. collected the data; S. C., E. D., and S. D. carried out the analysis; S. D. and E. D. drafted the manuscript. All authors read and approved the final version of the manuscript.

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