Candidemia in COVID-19 patients: incidence and characteristics in a prospective cohort compared to historical non-COVID-19 controls

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Dear Editor,

We have read with interest the article by Lewis White and Colleagues, providing insights on invasive fungal infections in COVID-19 patients [1]. The Authors describe a significant proportion of invasive yeast infections, especially candidemia. It is not clear to date if the incidence of candidemia in COVID-19 patients is higher than expected. Moreover, no comparison of clinical presentation and outcomes between affected patients with and without COVID-19 is available.

To investigate these points, we compared the incidence and characteristics of candidemia in a prospective cohort of patients with SARS-CoV-2 infection to those of a historical cohort of non-COVID-19 controls.

We included patients with candidemia (defined as one or more positive blood cultures for *Candida* spp*)* hospitalized at the San Raffaele Hospital (Milan, Italy) with COVID-19 from February, 15th to June 30th, 2020, or hospitalized for any reason from January, 1st to December, 31st 2017 (historical non-COVID-19 cohort). Ethical committee approved data collection for both cohort studies (34/INT/2020 and 29/INT/2020).

Pearson Chi-square test and Mann-Whitney U-test were applied, as appropriate. Incidence rate was calculated as events per 10.000 person-day of follow-up (PDFU) and compared by Poisson regression. Statistical analysis was performed with SPSS-v.20 (IBM, Chicago, USA).

We identified 21 and 51 patients in COVID-19 cohort and historical cohort, respectively (Table 1). Incidence rate of candidemia was significantly higher in patients with COVID-19 (10.97 [6.79 – 16.76] vs. 1.48 [1.10 – 1.95] cases per 10.000-PDFU. P-value <0.001).

Candida albicans was the most frequently involved pathogen, even though non-*albicans Candida* spp were detected in a considerable proportion of patients (33.3% vs. 47.1%, P-value 0.285). Infective endocarditis and endophthalmitis were rarely encountered. Candidemia clearance was obtained in

most patients (71.4% vs. 72.5%, P-value 0.923), but overall mortality was high (57.1% vs. 58.8%, P-value 0.895).

COVID-19 patients had a lower median Charlson comorbidity index, and no differences were detected in prior use of antibiotics, antifungal agents, parenteral nutrition or other conditions potentially predisposing to candidemia, except for a higher proportion of patients with solid malignancies and recent chemotherapies in the historical cohort. COVID-19 patients were more likely to be in ICU (66.7% vs. 29.4%, P-value 0.003), and treated with immunosuppressive agents (61.1% vs. 32.7%, P-value 0.035), but proportion of patients on glucocorticoids was not different (44.4%, vs. 30.6%, P-value 0.291). When calculating incidence rate only on ICU patients, this was still markedly higher in COVID-19 patients (81.68 [44.46 – 137.10] vs. 14.46 [8.09 – 23.84] cases per 10.000 PDFU, P-value <0.001).

Limitations of this work include the monocentric retrospective design, and the limited sample size.

In conclusion, we observed an increased incidence of candidemia in hospitalized patients with COVID-19 compared to a historical non-COVID-19 cohort. We found no imbalance in several predisposing risk factors for candidemia, with the notable exception of a higher proportion of subjects in ICU and on immunosuppressive agents in the COVID-19 cohort. A COVID-19-induced predisposition to candidemia, possibly linked to previously reported alterations like immune paralysis, enhanced intestinal translocation[2] and switch of microbiota towards *Candida* spp.[3] should be explored in further studies.

NOTES

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Conflict of interests

Authors declare no relevant conflict of interests.

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Table legend

Table 1

Characteristics of the two cohorts of patients with candidemia.

	Overall	COVID-19	Non-COVID-19	*P*-value
	N=72	*N=21*	*N=51*	
Demographics				
Age, years	71 (61-77)	71 (57-75)	72 (61-80)	0.197
Sex, male	49 (68.1%)	16 (76.2%)	33 (64.7%)	0.342
Risk factors for candidemia				
Diabetes	15 (21.1%) *N=71*	2 (10.0%) *N=20*	13 (25.5%) *N=51*	0.150
Active hematological malignancy [a]	2 (2.8%) *N=71*	0 (0%) *N=20*	2 (3.9%) *N=51*	0.369
Active solid malignancy [a]	23 (32.4%) *N=71*	0 (0%)	23 (45.1%)	**<0.001**
Recent chemotherapy [b]	9 (12.7%) *N=71*	0 (0%)	9 (17.6%)	**0.044**
HIV infection	1 (1.4%) *N=71*	0 (0%)	1 (2.0%)	0.528
Charlson comorbidity index	5 (3-6) *N=71*	3 (1-3) *N=20*	5 (4-7) *N=51*	**<0.001**
Hemodialysis	9 (12.9%) *N=70*	4 (21.1%) *N=19*	5 (9.8%) *N=51*	0.211
ICU stay	29 (40.3%)	14 (66.7%)	15 (29.4%)	**0.003**
Prior use of broad spectrum antibiotics [c]	61 (87.1%) *N=70*	19 (100%) *N=19*	42 (82.4%) *N=42*	0.050
Prior use of antifungal agents [c]	12 (17.1%) *N=70*	2 (10.5%)	10 (19.6%)	0.370
Central venous catheters	53 (73.6%)	17 (81.0%)	36 (70.6%)	0.364
Parenteral nutrition	37 (53.6%) *N=69*	8 (44.4%) *N=18*	29 (56.9%) *N=51*	0.364
Immunosuppressive agents [d]	27 (40.3%) *N=67*	11 (61.1%) *N=18*	16 (32.7%) *N=49*	**0.035**

Steroid treatment [e]	23 (34.3%)	8 (44.4%)	15 (30.6%)	0.291
	N=67	*N=18*	*N=49*	
Candida colonization [f]	35 (48.6%)	8 (38.1%)	27 (52.9%)	0.252
Recent surgery [g]	25 (35.2%)	5 (25.0%)	20 (39.2%)	0.259
	N=71	*N=20*	*N=51*	
Laboratory examinations				
White blood cells, cells x 10^9/mL	9.9 (6.6-14.1)	9.1 (7.0-12.8)	10.3 (6.1-15.4)	0.838
Neutrophils, cells x 10^9/mL	6.9 (4.4-11.3)	6.9 (4.2-11.2)	7.7 (4.6-12.0)	0.795
	N=59	*N=17*	*N=42*	
Lymphocytes, cells x 10^9/mL	0.7 (0.5-1.0)	0.7 (0.7-1.0)	0.6 (0.4-1.0)	0.199
	N=59	*N=17*	*N=42*	
Creatinine, mg/dL	1.1 (0.7-1.7)	1.0 (0.7-1.6)	1.2 (0.8-1.8)	0.620
Clinical course and outcomes				
Days to candidemia since hospital admission	20 (8-33)	24 (12-38)	18 (7-30)	0.187
Fungemia clearance [h]	52 (72.2%)	15 (71.4%)	37 (72.5%)	0.923
Days to candidemia clearance	8 (5-12)	6 (5-17)	8 (5-12)	0.662
	N=52	*N=15*	*N=37*	
Non-albicans candidemia	31 (43.1%)	7 (33.3%)	24 (47.1%)	0.285
Endocarditis	5 (12.5%)	2 (13.3%)	3 (12.0%)	0.902
	N=40	*N=15*	*N=25*	
Endophthalmitis	2 (11.1%)	2 (25.0%)	0 (0%)	0.094
	N=18	*N=8*	*N=10*	
Death	42 (58.3%)	12 (57.1%)	30 (58.8%)	0.895
Incidence rate, per 10.000-PDFU	1.98 (1.55-2.49)	10.97 (6.79-16.76)	1.48 (1.10-1.95)	**<0.001**

Values are reported as median, interquartile range or frequency (%).

N: number of patients; HIV: Human Immunodeficiency Virus; ICU: intensive care unit; PDFU: person-day follow-up.

a: <5 years of negative follow-up since the last potentially curative intervention;

b: administration of chemotherapies during the 90 days before candidemia;

c: administration of antimicrobials during the 14 days before candidemia;

d: administration of immunomodulating drugs (anakinra, tocilizumab, reparixin, mavrilimumab, sarilumab) and/or immunosuppressive drugs (cyclophosphamide, tacrolimus, mycophenolate) in the last 30 days before candidemia;

e: administration of 0.5 to 1 mg/kg of prednisone equivalent in the last 30 days before candidemia;

f: positive Candida spp. culture from non-sterile site sand/or clinical signs and symptoms compatible with skin or mucous membranes fungal infection;

g: any major surgical procedure in the last 30 days;

h: two negative sets of blood cultures collected after at least 48 hours from initiation of an appropriate therapy.