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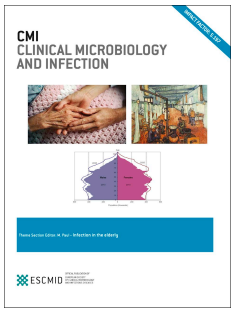

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Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients– a multinational observational study by the European Confederation of Medical Mycology

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CAPA in critically-ill COVID-19 patients

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Abstract

Objectives

Coronavirus disease 2019 (COVID-19) associated pulmonary aspergillosis (CAPA) has emerged as a complication in critically ill COVID-19 patients. The objectives of this multinational study were to determine the prevalence of CAPA in patients with COVID-19 in intensive care units (ICU) and to investigate risk factors for CAPA as well as outcome.

Methods

The European Confederation of Medical Mycology (ECMM) conducted a multinational study including 20 centers from nine different countries to assess epidemiology, risk factors, and outcome of CAPA. CAPA was defined according to the 2020 ECMM/ISHAM consensus definitions.

Results

A total of 592 patients were included in this study, including 11 (1.9%) patients with histologically proven CAPA, 80 (13.5%) patients with probable CAPA, 18 (3%) with possible CAPA and 483 (81.6%) without CAPA. CAPA was diagnosed a median of 8 days (range 0-31) after ICU admission predominantly in older patients [adjusted hazard ratio (aHR) 1.04 per year; 95%CI 1.02-1.06] with any form of invasive respiratory support (HR 3.4; 95%CI 1.84-6.25) and receiving tocilizumab (HR 2.45; 95%CI 1.41-4.25). Median prevalence of CAPA per center was 10.7% (range 1.7%-26.8%). CAPA was associated with significantly lower 90-day ICU survival rate (29% in patients with CAPA versus 57% in patients without CAPA; Mantel-Byar $p<0.001$) and remained an independent negative prognostic variable after adjusting for other predictors of survival (HR=2.14; 95%CI: 1.59-2.87, $p<=0.001$).

Conclusion

Prevalence of CAPA varied between centers. CAPA was significantly more prevalent among older patients, patients receiving invasive ventilation and patients receiving tocilizumab, and was an independent strong predictor of ICU mortality.

Key Words: CAPA, COVID-19, Aspergillus, ICU, Survival

Introduction

The release of danger-associated molecular patterns (DAMPs) during coronavirus disease-19 (COVID-19) acute respiratory failure (ARF) may contribute to a highly permissive inflammatory environment that favors pathogenesis of COVID-19 associated pulmonary aspergillosis (CAPA)[1, 2]. CAPA has first been described in early 2020 in case reports or small case series[3-5]. Since then, larger case series and cohorts have followed[1, 6-10] and CAPA is now considered a potential life-threatening secondary infection in a significant number of critically ill COVID-19 patients[11]. Reported CAPA prevalence rates vary widely between different studies (3% - 33%)[12-16]. Several factors may explain the wide variation of CAPA rates including differences in awareness and local diagnostic strategies (e.g., bronchoscopies not done[17]), as well as various different criteria applied for definition of aspergillosis in COVID-19 patients[16, 18].

The recently published consensus criteria for definition of CAPA[19] will lead to more uniform CAPA classification across studies and will thereby increase comparability of results. According to those consensus criteria, diagnosis of CAPA relies on microbiological work-up, clinical characteristics, and imaging studies, however, diagnosis of CAPA remains a complex clinical challenge[20].

Several risk factors for CAPA have been described in single center cohorts, including azithromycin use, use of corticosteroids, use of anti-interleukin-6 treatment and underlying pulmonary disease[6, 7, 21, 22], however, for identification of factors that would allow for targeted prevention efforts larger prospective cohort studies are needed. While some single center studies have reported that CAPA was associated with higher mortality rates[6, 7], larger studies are needed to elucidate the role of CAPA in overall mortality in COVID-19 ARF.

To determine the prevalence of CAPA in patients with COVID-19 in ICUs and to investigate risk factors for CAPA as well as potential associations with mortality, the ECMM has initiated a multicenter, multinational cohort study comparing risk factors, and clinical outcomes in patients with COVID-19 associated ARF with and without CAPA.

Methods

Study design and participating centers

We performed a multicenter, multinational cohort study including 20 centers in nine countries: Austria (n=2), Belgium (n=4), France (n=3), Germany (n=4), Italy (n=2), Pakistan (n=1), Spain (n=1), United Kingdom (n=1) and United States (n=2). The main objectives of this study were to assess the epidemiology of CAPA, risk factors associated with development of CAPA and outcomes of patients with CAPA on intensive care unit (ICU). The study was initiated in March 2020 and data entry was open until May 2021.

All participating centers were invited to provide data on demographics, underlying medical conditions, risk factors for invasive fungal infections, details on diagnostic work-up (including radiological and microbiological data), treatment and outcome via an online case report form. Based on the dynamic evolution of the COVID-19 pandemic in 2020 the study protocol did not include target enrollment numbers per participating center. Among the 20 participating centers, eight (Medical University of Graz; all five centers in Belgium, University of Cologne; San Martino Polyclinic Hospital Genoa; University of Manchester) provided prospectively collected data (different time periods between March 2020 to April 2021) on all consecutive COVID-19 patients (i.e., during the center specific different enrollment periods) admitted to an ICU enabling calculation of CAPA prevalence. The remaining twelve centers provided data for limited numbers of CAPA cases and/or patients without CAPA only.

Inclusion criteria were as follows: I.) Adults (≥18 years) with polymerase chain reaction (PCR) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and II.) ICU admission due to COVID-19 associated ARF. Exclusion criteria was ICU admission due to other conditions besides COVID-19 ARF.

For data acquisition and storage, we used FungiScope® (NCT 01731353), providing an anonymized electronic case report form accessible through www.clinicalsurveys.net [23]. Results on treatment and

diagnosis[24] as well as a few of the included CAPA cases have been published in the meantime [5, 24-26].

For classification of cases, we used the 2020 ECMM/ISHAM consensus criteria[19]. According to the criteria, patients were categorized as either proven pulmonary and/or tracheobronchial CAPA, probable pulmonary and/or tracheobronchial CAPA, possible pulmonary and/or tracheobronchial CAPA or no evidence for CAPA.

Statistical analysis and ethics

All statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) and Stata (Windows version 16.0, Stata Corp., Houston, TX, USA). Baseline characteristics between patients with and without disease progression or death during follow-up were compared with rank-sum tests, χ^2-tests, and Fisher's exact tests, as appropriate. Median follow-up was computed according to the method of Schemper and Smith, and overall survival with a Kaplan-Meier estimator. For comparison of survivor functions between the two study groups, we used log-rank tests. To investigate the association of risk factors with survival, uni- and multivariable Cox models were estimated. The proportionality of hazard assumption was evaluated by fitting an interaction between a variable of interest and linear follow-up time. To eliminate immortal time bias, time from CAPA diagnosis was modelled as a so-called time-dependent variable within Cox models. This was achieved by partitioning the follow-up time of patients who did and did not develop CAPA. For visual display of the association between the groups, we performed landmark analyses after 14 days after ICU admission. A p value of < 0.05 was considered statistically significant. For calculation of CAPA prevalence, the number of patients diagnosed with CAPA according to the definitions was divided by the total number of COVID-19 patients on ICU presenting during the study period (for prospective cohorts only). Each participating study center was responsible to obtain local institutional review board (IRB) approval, if required by local ethics policy. For the eight centers with data collection on all consecutive ICU patients IRB approval numbers are as following: Medical University of Graz EC #32-296 ex 19/20; University of Genoa Liguria Region Ethics

Committee registry number 163/2020; for the centers from Belgium the study was approved by ethical board of the University Hospital Leuven (S64071); at the University of Cologne patients were included in the FungiScope® global registry which was approved by the local ethics committee of the University of Cologne, Cologne, Germany (identifier 05-102); at the University of Manchester data acquisition was conducted as a retrospective audit which does not require local ethics but was approved by the Hospital's audit committee. All centers followed local ethical requirements. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

A total of 592 patients with PCR confirmed SARS-CoV-2 infection requiring ICU admission due to COVID-19 associated acute respiratory failure have been included in this study. Numbers of included patients per center are displayed in **Figure 1**. Out of the 592 included patients, eleven (1.9%) had histologically proven CAPA, 80 (13.5%) had probable CAPA, 18 (3%) had possible CAPA and 483 (81.6%) had no evidence for CAPA. CAPA prevalence was estimated from cases entered by eight of the participating centers which have entered all consecutively enrolled COVID-19 ICU patients with CAPA [n=57 (six proven, 48 probable, three possible)] and without CAPA (n=475). CAPA prevalence between the eight centers ranged from 1.7% (Roeselare, Belgium) to 26.8% (Antwerp, Belgium and Cologne, Germany) for proven, probable or possible CAPA.

Characteristics of the Study Cohort

Table 1 displays differences in demographic and clinical characteristics and outcomes between patients with CAPA and those without. CAPA was diagnosed after a median of 8 days (25-75th Percentile: 4 – 13) after ICU admission. Patients who were diagnosed with CAPA were older, more often male, and did more frequently receive invasive mechanical ventilation (**Table 1**). Patients who developed CAPA during ICU treatment received more frequently tocilizumab, while there was no difference in the use of systemic corticosteroids.

Systemic antifungal treatment was initiated in 99 out of 109 patients with CAPA (90.7%) and 52% of those were alive at ICU discharge versus 10% of those not receiving antifungal treatment. Among those who received antifungal monotherapy with voriconazole or isavuconazole 33/50 (66%) survived at ICU discharge and 34/65 (52%) survived at Day 84.

Uni- and multivariable predictors of CAPA

In the univariable time-to-90-day CAPA Cox regression model older age (HR 1.18; 95%CI: 1.08-1.28 per year), any kind of invasive respiratory support (which displays a composite variable from invasively ventilated patients and patients receiving extracorporeal membrane oxygenation) (HR 2.93; 1.60-1.50) and the administration of tocilizumab (HR 2.34; 1.35-4.06) were associated with significantly higher risk for developing CAPA (**Table 2**). When including the specific study centres in our Cox-model to account for local differences in CAPA incidence, this failed to influence CAPA incidence significantly (HR 1.02; 0.99-1.05 for participating centre). We then included all univariable predictors of CAPA in multivariable Cox-models where age (HR: 1.04; 1.02-1.06 per year), any kind of invasive respiratory support (HR 3.4; 1.84-6.25) and tocilizumab treatment (HR 2.45; 1.41-4.25) remained independent predictors of 90-day CAPA.

Survival in those with and without CAPA

Overall, 261 deaths were observed. In the re-applied univariable Cox models for time-to-90 days ICU survival development of CAPA (HR 1.36; 1.02-1.81), older age (HR 1.24; 1.17-1.31 per year), the participating centre (HR 0.96; 0.95-0.98), active malignant disease (HR 1.68; 1.12-2.51), solid organ transplantation (HR 1.89, 1.04-3.46), cardiovascular disease (HR 1.33; 1.04-1.72), diabetes mellitus (HR, 1.44; 1.11-1.86) and a history of smoking (HR 1.58, 1.12-2.24) were univariable predictors of worse 90-day-ICU outcomes.

To control for immortal time, i.e. time between ICU admission and CAPA diagnosis where patients cannot die from CAPA, we used a multistate regression model in which ICU-survival time was divided into survival before CAPA diagnosis and survival after CAPA diagnosis. The model showed that patients who developed CAPA during their ICU stay displayed worse outcomes regarding 90-day ICU survival (HR=2.14, 95%CI: 1.59-2.87, $p<=0.001$). CAPA remained an independent negative prognostic variable after adjusting this post-event data for important univariable predictors of survival (**Table 3**). In a landmark analysis after 14 days, 90-day ICU survival estimates were 57% (95%CI: 52-62) in patients who

were not diagnosed with CAPA and 29% (95%CI: 19-39) in patients who were diagnosed with CAPA during their ICU stay (Mantel-Byar; *p<0.001*, **Figure 2**).

Discussion

We performed a large multinational study on CAPA in critically ill COVID-19 patients and found that prevalence varied widely between centers with a median prevalence of 11%. CAPA was diagnosed at a median of 8 days after ICU admission and was more often diagnosed in elderly patients who needed invasive ventilation and received tocilizumab. CAPA was associated with devastating mortality, and remained an independent negative prognostic variable after adjusting for other predictors of survival

The true prevalence of CAPA is still a matter of debate and depends on various factors including socioeconomic factors (e.g. general health condition of a population; access to healthcare institutions, etc.), local epidemiology and/or seasonal variations in the spread of *Aspergillus* spores[27], local awareness regarding fungal infections in critically ill patients and the availability and turnaround time of diagnostic tools to diagnose CAPA (e.g. bronchoscopies[17], easy access to CT-scans, fungal biomarkers, etc.), and also criteria used for classification of CAPA. The importance of bronchoscopy was highlighted in this cohort where galactomannan testing from BALF had higher sensitivity (77% with 1.0 ODI cutoff) than from serum (19%)[24]. In this study we have classified all patients according to the recently published standardized ECMM/ISHAM consensus definitions for CAPA[19], and found a median CAPA prevalence among the participating centers of 10.7%, ranging between 1.7% and 26.8%. This range is similar to the reported CAPA rates in the literature so far, even if a wide range of definitions had previously been used[8].

Understanding the main drivers and risk factors for development of CAPA is important, to be able to better target aggressive screening or even use of antifungal prophylaxis to prevent CAPA in high risk COVID-19 patients. In our multivariable model need for invasive ventilation, older age and treatment with tocilizumab were significantly associated with increased probability of CAPA development. These variables may primarily reflect patients with more severe COVID-19, more severe lung damage and impaired immune response in the elderly. However, other factors described before to be associated with CAPA development like the use of systemic corticosteroids[7], or the use of azithromycin[21], were not

significantly associated with CAPA in our study. Whereas, corticosteroids are a well-known risk factor for impaired neutrophil function and thus development of invasive fungal infections, it is now considered standard of care treatment in critically ill COVID-19 patients and therefore less likely to turn out as significant predictor of CAPA[28]. Indeed, the majority of patients with severe COVID-19 in this study received systemic corticosteroids, which is in contrast to some of the earlier studies where use of systemic corticosteroids was less frequent[6, 7, 29]. Tocilizumab turned out as risk factor for CAPA development in our cohort. The use of anti-IL-6 treatment or inhibition of Janus kinase seems to increase the overall risk of secondary infections in critically ill COVID-19 patients, but there was no convincing evidence from larger studies currently that risk for CAPA is increased by the use of anti-IL-6 treatment[6, 29], which is in contrast to our finding. Nevertheless, as treatment strategies for critical COVID-19 have changed several times within the last year, comparison among the different trials and different study centers is difficult, as is a potential impact of combinations of different immunosuppressive/immunomodulatory treatment regimens.

Some previous, single center studies, have indicated that CAPA may prolong stay in hospital and invasiveness of ventilation[29], and may also be associated with higher mortality compared to non-CAPA patients[6, 7], while others did not show any impact on mortality[12]. Our results show that CAPA was associated with a nearly 2-fold increased risk of ICU mortality compared to patients who did not develop CAPA (71% versus 43%), even after accounting for various other factors that impact mortality. This finding supports the hypothesis that CAPA development has negatives effects on overall outcome in critically ill COVID-19 patients. Whether or not, this is a causal association and therefore prevention of CAPA by applying antifungal prophylaxis strategies may improve the overall outcome of these patients, needs to be clarified in future, randomized-controlled trials (RCT). For influenza associated invasive aspergillosis results of a RCT were recently published that showed no significant benefit of prophylaxis due to the fact that invasive aspergillosis often occurred within few hours of ICU admission[30]. Given that CAPA seems to develop later, prophylaxis may be more promising.

This multicenter multinational study comes along with several limitations. Presented data reflect a real-life scenario with no predefined CAPA screening, fungal diagnostics strategies or treatment protocols. Also, the study was initiated in March 2020 and data entry was closed in May 2021. However, despite enrolling prospectively not all centers had CAPA and non-CAPA patients reported for the entire study period. Due to changes in diagnostic strategies for CAPA as well as treatment strategies for critically ill COVID-19 patients, this might have influenced our findings and generalizability. Detailed data on dosage and frequency of tocilizumab administration was not available from all centers, although the majority appeared to have used 8mg/kg bodyweight. Some centers only entered few cases and/or controls, and those data had therefore to be excluded from calculation of CAPA prevalence. CAPA prevalence may have been underestimated due to the fact that a minority (<6%) of patients without CAPA have received antifungal prophylaxis or empirical therapy. In addition, time from ICU admission to CAPA development may have been underestimated, as external ICU stays that occurred before the admission into the current ICU may not have been covered in our database. Finally, month of diagnosis and some other data were not available for all patients.

In conclusion, CAPA was more often diagnosed in elderly patients, in patients who needed invasive ventilation and in patients who received tocilizumab and was strongly associated with mortality, remaining an independent negative prognostic variable after adjusting for other predictors of survival. Future studies should evaluate whether antifungal prophylaxis may reduce CAPA prevalence.

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Substantial contribution to the acquisition of data for the work: J.P., J.W., D.R.G., J.S.-G., M.B., M.R., L.R., N.v.R, P.L., S.F., A.C.R., T.L., M.V., L.D., K.J., J.S., S.H., A.R., M.C., M.H.

Substantial contribution to the statistical analysis or interpretation of data: J.P., J.W., D.R.G., S.H., K.L., R.R.R., M.H.

Drafting the manuscript: J.P., D.R.G., S.H., K.L., M.H.

Critical review of the manuscript and final approval for publication: all authors

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Conflicts of Interest

JP has received personal fees from Gilead Sciences and Pfizer, research funding from MSD outside of the submitted work and is stoke holder of AbbVie Inc and Novo Nordisk.

JW reports grants and personal fees from Gilead and Pfizer: investigator-initiated grants, personal fees and also on-financial support from MSD, outside the submitted work.

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JS has received lecture honoraria from Gilead and Pfizer, outside of the submitted work.

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All other authors declare no conflict of interest for this study.

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Table 1: Demographic Data and Characteristics of patients with and without CAPA

	Total (N=592)[#]	**CAPA group*** **(N=109)**[#]	**Non-CAPA group** **(N=483)**[#]	**p-value****
Age (median, 25-75th Percentile)	64 (55 – 73)	68 (60 – 75)	63 (54 – 73)	0.003
Female Sex, N (%)	173 (29.2)	23 (21.1)	150 (31.1)	0.039
Underlying Diseases				
Cardiovascular disease, N (%)	329 (55.6)	63 (57.8)	266 (55.1)	n.s.
Diabetes mellitus, N (%)	160 (27.0)	32 (29.4)	128 (26.5)	n.s.
History of smoking, N (%)	66/587 (11.2)	14/105 (13.3)	52/482 (10.8)	n.s.
Active malignant disease, N (%)[$]	43 (7.3)	11 (10.3)	32 (6.6)	n.s.
Obesity (BMI >30 kg/m^2), N (%)	168/544 (30.9)	24/85 (28.2)	144/459 (31.4)	n.s
Pulmonary disease, N (%)	113 (19.1)	26 (23.9)	87 (18.0)	n.s.
Solid organ transplantation, N (%)	14 (2.4)	5 (4.9)	9 (1.9)	n.s.
Maximal Ventilation on ICU				
Non-invasive Ventilation, N (%)	218/584 (37.3)	14/103 (13.6)	204/481 (42.4)	<0.001
Invasive Mechanical Ventilation, N (%)	418/591 (70.7)	96/109 (88.1)	322/482 (66.8)	<0.001
ECMO, N (%)	49/587 (8.3)	8/106 (7.5)	41/481 (8.5)	n.s.
Any Invasive Ventilation	419/587 (71%)	93/106 (88%)	326/481 (68%)	<0.001
COVID-19 Treatment				
Azithromycin, N (%)	75/296 (25.3)	11/62 (17.7)	64/234 (27.4)	n.s.
Corticosteroids systemic, N (%)	346/585 (59.1)	68/109 (62.4)	278/476 (58.4)	n.s.
Tocilizumab, N (%)	39/581 (6.7)	15/104 (14.4)	24/477 (5.0)	0.001

Survival Day 28, N (%)	380/583 (65.2)	64/105 (61.0)	316/478 (66.1)	n.s.
Survival Day 84, N (%)	333/592 (56.3)	48/109 (44.0)	285/483 (59.0)	0.004
Survival at ICU Discharge, N (%)	337/572 (58.9)	43/89 (48.3)	294/483 (60.9)	0.027
Survival End of Follow-Up, N (%)[$$]	327 (55.4)	47 (45.2)	280 (58.0)	0.008
ICU Stay, Days (median, 25-75th Percentile)	16 (7 – 29)	27 (17 – 42)	14 (6 – 27)	<0.001

Abbreviations: CAPA = COVID-19 associated pulmonary aspergillosis; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; N = Number; n.s. = not significant (p >0.05)

* including proven, probable and possible CAPA

** CAPA group versus non-CAPA group; only displayed if <0.05

[#] All % calculated for 592, 109 or 483 patients, respectively, unless stated otherwise. In case % were calculated for less than the maximal number of patients, data for some patients were missing and the actual denominator is displayed

[$] active malignancy is defined as solid malignancies for which treatment had been administered within six months (7/43) or hematological cancer that is not in complete remission (36/43).

[$$] maximal follow-up was 384 days from ICU admission

Table 2. Univariable and multivariable Cox Regression models for development of CAPA within 90-days.

Variable	Univariable Hazard Ratio	95%CI	P- value
Demographic variables			
Age (per 5 years)	1.18	1.08-1.28	**<0.001**
Female Gender	0.68	0.42-1.09	0.117
Study Centre	1.02	0.99-1.05	0.071
Coexisting conditions			
Number of coexisting conditions	0.92	0.76-1.10	0.380
Obesity	0.89	0.54-1.44	0.638
Active malignant disease	1.56	0.81-3.00	0.181
Solid organ transplantation	2.20	0.90-5.42	0.084
Cardiovascular disease	1.20	0.81-1.78	0.348
Pulmonary disease	1.42	0.89-2.24	0.133
Diabetes	1.12	0.73-1.73	0.605
History of smoking	1.36	0.76-2.44	0.293
Maximum Ventilation			
vvECMO (included in any invasive respiratory support)	0.80	0.37-1.70	0.547
Invasive ventilation (included in any invasive respiratory support)	2.53	1.53-4.17	**<0.001**
Non-Invasive ventilation	0.08	0.02-0.33	**<0.001**
Any invasive respiratory support	2.93	1.60-5.35	**<0.001**
Specific Medication			
Glucocorticoids	1.01	0.68-1.50	0.962
Tocilizumab	2.34	1.35-4.06	**0.002**
Azithromycin	0.63	0.33-1.21	0.167

Variable	Multivariable Hazard Ratio	95%CI	P- value
Age per year	1.04	1.02-1.06	**<0.001**
Any invasive respiratory support	3.40	1.84-6.25	**<0.001**
Tocilizumab	2.45	1.41-4.25	**<0.001**

Table 3 Univariate and multivariable Cox Regression models for 90-day ICU mortality.

Univariate Model	**Variable**	**Univariable Hazard Ratio**	**95%CI**	**P**
	Demographic variables			
	CAPA	1.36	1.02-1.81	<0.001
	Age (per 5 years)	1.24	1.17-1.31	<0.001
	Female Gender	1.07	0.82-1.39	0.607
	Study Centre	0.96	0.95-0.98	<0.001
	Coexisting conditions			
	Number of coexisting conditions	1.11	0.99-1.24	0.05
	Obesity	0.77	0.58-1.02	0.076
	Active malignant disease	1.68	1.12-2.51	0.013
	Solid organ transplantation	1.89	1.04-3.46	0.038
	Cardiovascular disease	1.33	1.04-1.72	0.021
	Pulmonary disease	1.35	0.98-1.77	0.060
	Diabetes mellitus	1.44	1.11-1.86	0.001
	History of smoking	1.58	1.12-2.24	0.001
	Maximum Respiratory Treatment			
	ECMO	0.99	0.65-1.51	0.982
	Invasive mechanical ventilation	1.05	0.81-1.35	0.708
	Non-Invasive ventilation	0.86	0.62-1.19	0.361
Multivariable Model	**Variable**	**Multivariable Hazard Ratio**	**95%CI**	**p**
#1 (n=592)	**CAPA**	1.77	1.31-2.37	<0.001
	Age	1.04	1.03-1.05	<0.001

#2 (n=592)	**CAPA**	2.23	1.66-2.99	<0.001
	Study center	0.96	0.94-0.98	<0.001
#3 (n=592)	**CAPA**	1.97	1.46-2.67	<0.001
	Active malignancy	1.47	0.98-2.23	0.062
	Solid organ transplantation	1.38	0.74-2.58	0.304
	Cardiovascular disease	1.19	0.92-1.54	0.178
	Diabetes mellitus	1.31	1.00-1.72	0.047
	History of smoking	1.46	1.02-.208	0.037
#4 (n=592)	**CAPA**	1.68	1.23-2.28	0.001
	Age	1.04	1.03-1.06	<0.001
	Study centre	0.95	0.94-0.97	<0.001
	Active malignancy	1.30	0.86-1.97	0.207
	Solid organ transplantation	1.59	0.85-2.98	0.145
	Cardiovascular disease	0.84	0.64-1.09	0.204
	Diabetes mellitus	1.36	1.04-1.78	0.022
	History of smoking	1.50	1.04-2.15	0.028

Abbreviations: 95% CI = 95% confidence interval; CAPA = COVID-19 associated pulmonary aspergillosis; ECMO =extracorporeal membrane oxygenation

Figure 1. Map of participating centers and numbers of CAPA cases (black semicircle) and cases without CAPA (white semicircle) entered per center. Centers from Europe and centers from the United States and Pakistan are displayed.

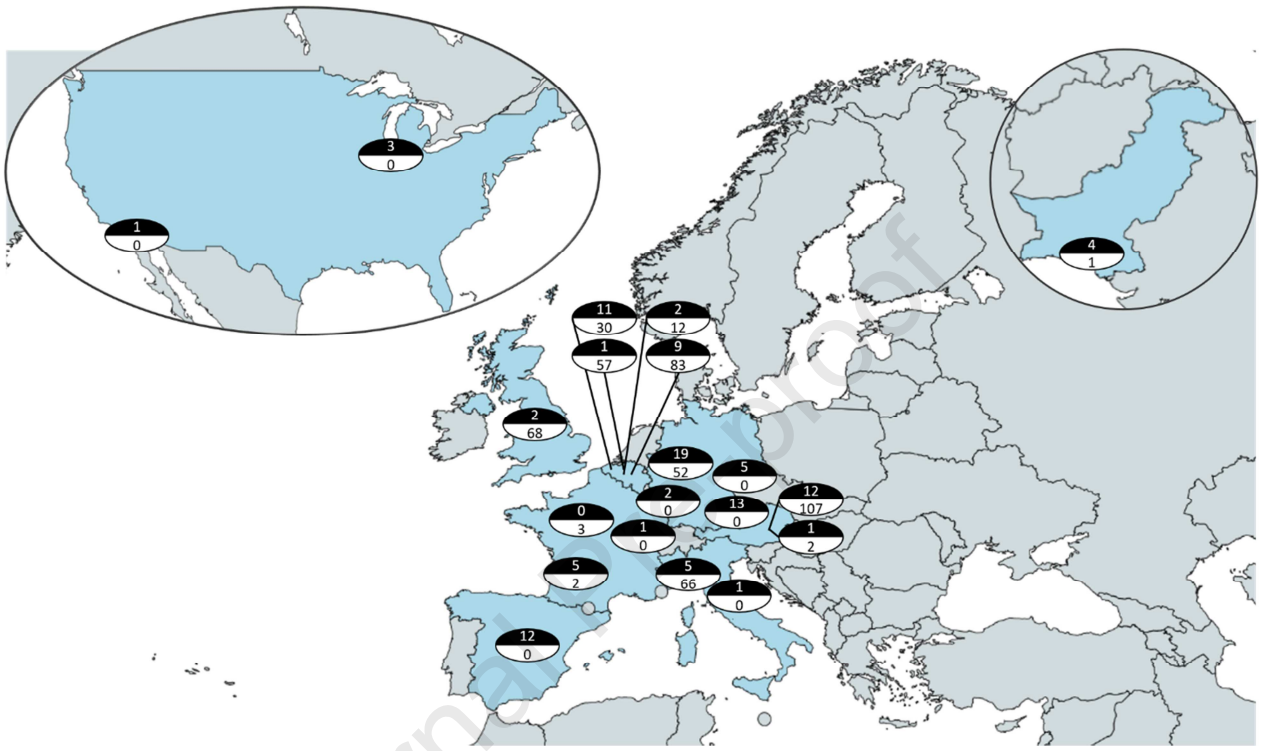

Figure 2. ICU survival in patients diagnosed with CAPA and patients who were not. Landmark analysis after 14 days for 90-day survival.