

Supplemental Material

Invasive aspergillosis in critically ill patients with influenza admitted to the intensive care unit: a prospective, multicentre cohort study

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Supplementary Methods

We applied the expert opinion case definition criteria for influenza-associated pulmonary aspergillosis as follows [1]:

1. Total influenza and niCAP cohorts: All included patients with influenza and niCAP.
2. Classifiable influenza and niCAP cohorts: Only patients who underwent any of the defined mycological tests and radiological imaging; those who did not were regarded not classifiable. In case of an unknown mycological or radiological result, patients were not classifiable unless the other criterion was known to be negative. Those who did not undergo bronchoscopy were not classifiable for invasive tracheobronchial aspergillosis (ITBA), but could still be classifiable for pulmonary IAPA/IPA.
3. Patients with IAPA/IPA: Only classifiable patients fulfilling criteria for proven or probable IAPA/IPA. Classifiable patients with negative mycological and/or radiological criteria were classified as No IAPA/IPA. Patients were assessed for subsets A and B of the IAPA criteria independently. In our study, patients not classifiable for subset A and not meeting criteria for subset B all demonstrated infiltrates on imaging. Hence, they were regarded as not classifiable. Patients with proven and probable ITBA and IAPA/IPA were combined into IAPA/IPA groups, unless stated otherwise.

Supplementary Table 1. Supplemental data on the total, classifiable and IAPA/no IAPA population

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Baseline characteristics											
Median age (years)	66 (56 – 74)	65 (55 – 72)	68 (60 – 75)	0.043	66 (55 – 74)	65 (54 – 72)	70 (60 – 76)	0.015	65 (56 – 68)	65 (53 – 74)	0.43
Male sex	179/292 (61.3%)	101/174 (58.0%)	78/118 (66.1%)	0.18	139/216 (64.4%)	82/140 (58.6%)	57/76 (75.0%)	0.018	22/34 (64.7%)	60/106 (56.6%)	0.43
Ethnicity - Caucasian	184/199 (92.5%)	111/123 (90.2%)	73/76 (96.1%)	0.17	138/151 (91.4%)	96/106 (90.6%)	42/45 (93.3%)	0.76	24/24 (100%)	72/82 (87.8%)	0.11
Ethnicity – Northern African	3/199 (1.5%)	2/123 (1.6%)	1/76 (1.3%)	1.00	3/151 (2.0%)	2/106 (1.9%)	1/45 (2.2%)	1.00	0/24 (0%)	2/82 (2.4%)	1.00
Ethnicity – Middle Eastern	7/199 (3.5%)	6/123 (4.9%)	1/76 (1.3%)	0.25	5/151 (3.3%)	4/106 (3.8%)	1/45 (2.2%)	1.00	0/24 (0%)	4/82 (4.9%)	0.57
Ethnicity – Black or Sub-Saharan African	2/199 (1.0%)	2/123 (1.6%)	0/76 (0%)	0.53	2/151 (1.3%)	2/106 (1.9%)	0/45 (0%)	1.00	0/24 (0%)	2/82 (2.4%)	1.00
Ethnicity – Asian	2/199 (1.0%)	1/123 (0.8%)	1/76 (1.3%)	1.00	2/151 (1.3%)	1/106 (0.9%)	1/45 (2.2%)	0.51	0/24 (0%)	1/82 (1.2%)	1.00
Ethnicity – Hispanic or Latino	1/199 (0.5%)	1/123 (0.8%)	0/76 (0%)	1.00	1/151 (0.7%)	1/106 (0.9%)	0/45 (0%)	1.00	0/24 (0%)	1/82 (1.2%)	1.00
Height (m)	1.73 (1.65 – 1.80) (n = 281)	1.72 (1.65 – 1.80) (n = 163)	1.74 (1.65 – 1.80)	0.82	1.74 (1.65 – 1.80) (n = 208)	1.73 (1.65 – 1.80) (n = 132)	1.75 (1.66 – 1.80)	0.98	1.75 (1.70 – 1.81)	1.72 (1.65 – 1.80) (n = 98)	0.28
Weight (kg)	76.0 (65.0 – 90.0) (n = 291)	80.0 (67.0 – 90.5) (n = 173)	74.1 (60.8 – 88.5)	0.031	76.0 (65.0 – 90.0) (n = 215)	80.0 (67.0 – 92.0) (n = 139)	74.6 (57.3 – 89.5)	0.06	79.5 (69.0 – 89.8)	80.0 (66.5 – 93.9) (n = 105)	0.76
BMI (kg/m ²)	25.2 (22.3 – 29.4) (n = 280)	26.0 (22.7 – 30.5) (n = 162)	24.7 (21.1 – 28.1)	0.035	25.0 (22.0 – 29.9) (n = 207)	25.5 (22.7 – 30.4) (n = 131)	24.5 (20.6 – 29.2)	0.07	25.7 (22.7 – 29.4)	25.0 (22.6 – 30.7) (n = 97)	0.92
BSA (m ²)	1.91 (1.76 – 2.08) (n = 194)	1.92 (1.77 – 2.10) (n = 115)	1.89 (1.75 – 2.02) (n = 79)	0.11	1.91 (1.75 – 2.08) (n = 145)	1.92 (1.77 – 2.10) (n = 99)	1.88 (1.67 – 2.02) (n = 46)	0.07	1.98 (1.87 – 2.09) (n = 24)	1.91 (1.73 – 2.12) (n = 75)	0.28
Influenza vaccination (season of ICU admission)	69/134 (51.5%)	31/70 (44.3%)	38/64 (59.4%)	0.09	54/107 (50.5%)	23/53 (43.4%)	31/54 (57.4%)	0.18	3/15 (20.0%)	20/38 (52.6%)	0.037
Smoking history	83/232 (35.8%)	56/133 (42.1%)	27/99 (27.3%)	0.026	64/175 (36.6%)	48/109 (44.0%)	16/66 (24.2%)	0.010	18/26 (69.2%)	30/83 (36.1%)	0.006
Days between hospital admission and ICU admission	0 (0 – 1) (n = 291)	1 (0 – 2) (n = 173)	0 (0 – 1)	< 0.001	1 (0 – 1) (n = 215)	1 (0 – 2) (n = 139)	1 (0 – 1)	0.037	1 (0 – 4)	0 (0 – 2) (n = 105)	0.008
Days of illness before hospital admission	3 (1 – 7) (n = 274)	4 (2 – 7) (n = 161)	3 (1 – 7) (n = 113)	0.30	4 (2 – 7) (n = 200)	4 (2 – 7) (n = 127)	3 (2 – 7) (n = 73)	0.92	7 (3 – 9) (n = 32)	3 (1 – 7) (n = 95)	0.003
Days of illness before ICU admission	5 (2 – 8) (n = 274)	5 (3 – 9) (n = 161)	4 (2 – 7) (n = 113)	0.020	5 (3 – 8) (n = 200)	6 (3 – 9) (n = 127)	4 (2 – 8) (n = 73)	0.30	9 (6 – 14) (n = 32)	4 (2 – 7) (n = 95)	< 0.001

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Any past medical history	268/290 (92.4%)	158/172 (91.9%)	110/118 (93.2%)	0.82	198/214 (92.5%)	125/138 (90.6%)	73/76 (96.1%)	0.18	29/34 (85.3%)	96/104 (92.3%)	0.31
Acute leukaemia < 90 days before admission	2/292 (0.7%)	2/174 (1.1%)	0/118 (0%)	0.52	2/216 (0.9%)	2/140 (1.4%)	0/76 (0%)	0.54	1/34 (2.9%)	1/106 (0.9%)	0.43
Acute leukaemia > 90 days before admission	3/292 (1.0%)	1/174 (0.6%)	2/118 (1.7%)	0.57	2/216 (0.9%)	1/140 (0.7%)	1/76 (1.3%)	1.00	0/34 (0%)	1/106 (0.9%)	1.00
SCT < 90 days before admission	1/289 (0.3%)	0/172 (0%)	1/117 (0.9%)	0.405	0/214 (0%)	0/139 (0%)	0/75 (0%)	NA	0/33 (0%)	0/106 (0%)	NA
SCT > 90 days before admission	9/289 (3.1%)	2/172 (1.2%)	7/117 (6.0%)	0.034	5/214 (2.3%)	2/139 (1.4%)	3/75 (4.0%)	0.35	1/33 (3.0%)	1/106 (0.9%)	0.42
Other haematological malignancy	22/292 (7.5%)	10/174 (5.7%)	12/118 (10.2%)	0.18	14/216 (6.5%)	7/140 (5.0%)	7/76 (9.2%)	0.25	4/34 (11.8%)	3/106 (2.8%)	0.06
Kidney transplantation	11/292 (3.8%)	6/174 (3.4%)	5/118 (4.2%)	0.76	8/216 (3.7%)	4/140 (2.9%)	4/76 (5.3%)	0.46	0/34 (0%)	4/106 (3.8%)	0.57
Lung transplantation	7/292 (2.4%)	5/174 (2.9%)	2/118 (1.7%)	0.71	5/216 (2.3%)	4/140 (2.9%)	1/76 (1.3%)	0.66	2/34 (5.9%)	2/106 (1.9%)	0.25
Heart transplantation	2/292 (0.7%)	1/174 (0.6%)	1/118 (0.8%)	1.00	1/216 (0.5%)	1/140 (0.7%)	0/76 (0%)	1.00	0/34 (0%)	1/106 (0.9%)	1.00
Pancreas or liver transplantation	1/292 (0.3%)	0/174 (0%)	1/118 (0.8%)	0.40	1/216 (0.5%)	0/140 (0%)	1/76 (1.3%)	0.35	0/34 (0%)	0/106 (0%)	NA
Cardiovascular disease	134/292 (45.9%)	83/174 (47.7%)	51/118 (43.2%)	0.47	103/216 (47.7%)	62/140 (44.3%)	41/76 (53.9%)	0.20	14/34 (41.2%)	48/106 (45.3%)	0.70
Diabetes mellitus	60/292 (20.5%)	37/174 (21.3%)	23/118 (19.5%)	0.77	41/216 (19.0%)	26/140 (18.6%)	15/76 (19.7%)	0.86	5/34 (14.7%)	21/106 (19.8%)	0.62
Asthma	17/292 (5.8%)	12/174 (6.9%)	5/118 (4.2%)	0.45	12/216 (5.6%)	10/140 (7.1%)	2/76 (2.6%)	0.22	0/34 (0%)	10/106 (9.4%)	0.12
COPD	79/292 (27.1%)	52/174 (29.9%)	27/118 (22.9%)	0.23	57/216 (26.4%)	41/140 (29.3%)	16/76 (21.1%)	0.20	9/34 (26.5%)	32/106 (30.2%)	0.83
Cystic fibrosis	0/292 (0%)	0/174 (0%)	0/118 (0%)	NA	0/216 (0%)	0/140 (0%)	0/76 (0%)	NA	0/34 (0%)	0/106 (0%)	NA
ILD/lung fibrosis	5/292 (1.7%)	3/174 (1.7%)	2/118 (1.7%)	1.00	3/216 (1.4%)	2/140 (1.4%)	1/76 (1.3%)	1.00	0/34 (0%)	2/106 (1.9%)	1.00
Pulmonary TB	2/291 (0.7%)	0/173 (0%)	2/118 (1.7%)	0.16	1/215 (0.5%)	0/139 (0%)	1/76 (1.3%)	0.35	0/34 (0%)	0/105 (0%)	NA
Multiple sclerosis	1/292 (0.3%)	1/174 (0.6%)	0/118 (0%)	1.00	1/216 (0.5%)	1/140 (0.7%)	0/76 (0%)	1.00	0/34 (0%)	1/106 (0.9%)	1.00
Liver cirrhosis	6/292 (2.1%)	5/174 (2.9%)	1/118 (0.8%)	0.41	4/216 (1.9%)	3/140 (2.1%)	1/76 (1.3%)	1.00	1/34 (2.9%)	2/106 (1.9%)	0.57
Ulcerative colitis	1/291 (0.3%)	0/173 (0%)	1/118 (0.8%)	0.41	1/215 (0.5%)	0/139 (0%)	1/76 (1.3%)	0.35	0/34 (0%)	0/105 (0%)	NA
Crohn's disease	1/291 (0.3%)	1/173 (0.6%)	0/118 (0%)	1.00	1/215 (0.5%)	1/139 (0.7%)	0/76 (0%)	1.00	0/34 (0%)	1/105 (1.0%)	1.00
Rheumatological disease/vasculitis/AID (excluding gout and osteoarthritis)	17/292 (5.8%)	10/174 (5.7%)	7/118 (5.9%)	1.00	11/216 (5.1%)	7/140 (5.0%)	4/76 (5.3%)	1.00	1/34 (2.9%)	6/106 (5.7%)	1.00
Psoriasis	1/292 (0.3%)	1/174 (0.6%)	0/118 (0%)	1.00	1/216 (0.5%)	1/140 (0.7%)	0/76 (0%)	1.00	1/34 (2.9%)	0/106 (0%)	0.24
HIV/AIDS	0/292 (0%)	0/174 (0%)	0/118 (0%)	NA	0/216 (0%)	0/140 (0%)	0/76 (0%)	NA	0/34 (0%)	0/106 (0%)	NA
Congenital immunodeficiency syndrome	1/289 (0.3%)	1/172 (0.6%)	0/117 (0%)	1.00	1/215 (0.5%)	1/139 (0.7%)	0/76 (0%)	1.00	1/34 (2.9%)	0/105 (0%)	0.24

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Acquired immunodeficiency syndrome other than HIV/AIDS	0/289 (0%)	0/172 (0%)	0/117 (0%)	NA	0/215 (0%)	0/139 (0%)	0/76 (0%)	NA	0/34 (0%)	0/105 (0%)	NA
Solid organ malignancy	46/291 (15.8%)	15/174 (8.6%)	31/117 (26.5%)	< 0.0001	39/215 (18.1%)	14/140 (10.0%)	25/75 (33.3%)	< 0.0001	3/34 (8.8%)	11/106 (10.4%)	1.00
Other malignancy	9/291 (3.1%)	6/174 (3.4%)	3/117 (2.6%)	0.74	6/215 (2.8%)	4/140 (2.9%)	2/75 (2.7%)	1.00	2/34 (5.9%)	2/106 (1.9%)	0.25
CKD requiring RRT	2/292 (0.7%)	1/174 (0.6%)	1/118 (0.8%)	1.00	2/216 (0.9%)	1/140 (0.7%)	1/76 (1.3%)	1.00	1/34 (2.9%)	0/106 (0%)	0.24
CKD not requiring RRT	19/292 (6.5%)	9/174 (5.2%)	10/118 (8.5%)	0.33	12/216 (5.6%)	5/140 (3.6%)	7/76 (9.2%)	0.12	1/34 (2.9%)	4/106 (3.8%)	1.00
Other	146/292 (50.0%)	86/174 (49.4%)	60/118 (50.8%)	0.91	112/216 (51.9%)	69/140 (49.3%)	43/76 (56.6%)	0.32	15/34 (44.1%)	54/106 (50.9%)	0.56
EORTC/MSGERC host factors											
Any EORTC host factor (2008 guidelines)	70/242 (28.9%)	38/144 (26.4%)	32/98 (32.7%)	0.31	55/187 (29.4%)	31/117 (26.5%)	24/70 (34.3%)	0.32	9/32 (28.1%)	22/85 (25.9%)	0.82
Recent neutropenia (< 0.5 x 10 ⁹ /L) > 10 days	1/240 (0.4%)	1/141 (0.7%)	0/99 (0%)	1.00	1/186 (0.5%)	1/115 (0.9%)	0/71 (0%)	1.00	0/31 (0%)	1/84 (1.2%)	1.00
Allogeneic stem cell transplant recipient	10/291 (3.4%)	3/173 (1.7%)	7/118 (5.9%)	0.10	7/216 (3.2%)	3/140 (2.1%)	4/76 (5.3%)	0.24	2/34 (5.9%)	1/106 (0.9%)	0.15
Solid organ transplant recipient	19/292 (6.5%)	11/174 (6.3%)	8/118 (6.8%)	1.00	13/216 (6.0%)	8/140 (5.7%)	5/76 (6.6%)	0.77	2/34 (5.9%)	6/106 (5.7%)	1.00
Recent history of prolonged corticosteroid use ^a	31/276 (11.2%)	21/162 (13.0%)	10/114 (8.8%)	0.34	22/204 (10.8%)	17/131 (13.0%)	5/73 (6.8%)	0.24	4/34 (11.8%)	13/97 (13.4%)	1.00
Median cumulative corticosteroid dose during 30 days or 4 weeks prior to ICU admission, mg/kg prednisone equivalent	2.78 (1.15 – 6.67) (n = 83)	3.29 (1.39 – 7.08) (n = 52)	2.55 (0.86 – 5.58) (n = 31)	0.33	2.73 (1.39 – 8.23) (n = 60)	3.33 (1.49 – 8.66) (n = 38)	2.55 (1.04 – 6.39) (n = 22)	0.39	9.36 (1.92 – 40.70) (n = 7)	3.13 (1.45 – 7.00) (n = 31)	0.30
T or B cell immunosuppressants (including cytotoxic chemotherapy) during 90 days prior to ICU admission	45/289 (15.6%)	20/172 (11.6%)	25/117 (21.4%)	0.031	34/214 (15.9%)	14/139 (10.1%)	20/75 (26.7%)	0.003	4/34 (11.8%)	10/105 (9.5%)	0.75
Inherited severe immunodeficiency	1/289 (0.3%)	1/172 (0.6%)	0/117 (0%)	1.00	1/215 (0.5%)	1/139 (0.7%)	0/76 (0%)	1.00	1/34 (2.9%)	0/105 (0%)	0.24
Microbiology before ICU admission											
Bacterial pathogens in respiratory samples during 30 days/4 weeks before ICU admission	17/206 (8.3%)	12/112 (10.7%)	5/94 (5.3%)	0.21	12/157 (7.6%)	9/93 (9.7%)	3/64 (4.7%)	0.36	2/26 (7.7%)	7/67 (10.4%)	1.00

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
<i>Aspergillus</i> cultured from respiratory samples during 6 months before ICU admission	3/220 (1.4%)	2/126 (1.6%)	1/94 (1.1%)	1.00	3/168 (1.8%)	2/104 (1.9%)	1/64 (1.6%)	1.00	1/28 (3.6%)	1/76 (1.3%)	0.47
Viruses isolated from respiratory samples during 30 days/4 weeks before ICU admission	30/230 (13.0%)	24/133 (18.0%)	6/97 (6.2%)	0.009	28/175 (16.0%)	23/110 (20.9%)	5/65 (7.7%)	0.031	6/28 (21.4%)	17/82 (20.7%)	1.00
Systemic antifungal use with anti- <i>Aspergillus</i> activity during 30 days or 4 weeks prior to ICU admission	2/274 (0.7%)	1/162 (0.6%)	1/112 (0.9%)	1.00	2/203 (1.0%)	1/131 (0.8%)	1/72 (1.4%)	1.00	0/33 (0%)	1/98 (1.0%)	1.00
Vital parameters and laboratory results at ICU admission											
APACHE II score	18 (14 – 26) (n = 129)	16 (13 – 25) (n = 67)	19 (14 – 26) (n = 62)	0.14	18 (14 – 26) (n = 96)	17 (14 – 26) (n = 48)	19 (14 – 27) (n = 48)	0.47	21 (15 – 29) (n = 17)	16 (13 – 23) (n = 31)	0.14
Core body temperature (°C)	37.6 (36.6 – 38.6) (n = 241)	37.6 (36.7 – 38.9) (n = 142)	37.6 (36.5 – 38.3) (n = 99)	0.17	37.6 (36.6 – 38.7) (n = 180)	37.7 (36.7 – 38.9) (n = 119)	37.6 (36.4 – 38.3) (n = 61)	0.08	37.6 (36.4 – 38.4) (n = 30)	37.8 (36.9 – 39.1) (n = 89)	0.23
MAP (mmHg)	70 (59 – 84) (n = 237)	70 (59 – 84) (n = 138)	68 (58 – 84) (n = 99)	0.64	70 (59 – 85) (n = 175)	71 (59 – 85) (n = 114)	70 (58 – 84) (n = 61)	0.71	80 (70 – 96) (n = 27)	68 (58 – 84) (n = 87)	0.026
Heart rate (bpm)	102 (80 – 122) (n = 239)	100 (79 – 122) (n = 140)	104 (86 – 122) (n = 99)	0.35	98 (77 – 120) (n = 177)	98 (79 – 122) (n = 116)	98 (73 – 117) (n = 61)	0.58	95 (75 – 112) (n = 29)	100 (80 – 125) (n = 87)	0.32
Respiratory rate (per minute)	27 (20 – 34) (n = 237)	26 (20 – 33) (n = 138)	28 (24 – 35) (n = 99)	0.022	27 (20 – 34) (n = 176)	26 (20 – 33) (n = 115)	28 (24 – 34) (n = 61)	0.20	27 (18 – 33) (n = 29)	26 (20 – 33) (n = 86)	0.60
FiO2 (%)	70 (47 – 90) (n = 229)	68 (45 – 80) (n = 132)	70 (50 – 90) (n = 97)	0.14	70 (50 – 89) (n = 170)	70 (46 – 80) (n = 109)	75 (58 – 100) (n = 61)	0.042	70 (50 – 90) (n = 31)	60 (40 – 80) (n = 78)	0.22
Peripheral SpO2 (%)	91 (87 – 94) (n = 195)	92 (88 – 95) (n = 117)	90 (85 – 94) (n = 78)	0.09	91 (86 – 94) (n = 147)	92 (88 – 95) (n = 101)	89 (84 – 92) (n = 46)	0.037	92 (87 – 94) (n = 23)	92 (88 – 95) (n = 78)	0.71
PaO2 (kPa)	9.08 (7.65 – 11.15) (n = 237)	9.32 (7.89 – 11.58) (n = 140)	8.50 (7.41 – 10.25) (n = 97)	0.018	8.90 (7.60 – 11.44) (n = 176)	9.27 (7.82 – 11.84) (n = 116)	8.10 (7.26 – 9.73) (n = 60)	0.011	9.00 (7.50 – 11.85) (n = 31)	9.33 (7.92 – 11.85) (n = 85)	0.53
Ventilatory support at time of ICU admission ^b	142/195 (72.8%)	81/119 (68.1%)	61/76 (80.3%)	0.07	109/147 (74.1%)	70/102 (68.6%)	39/45 (86.7%)	0.025	17/24 (70.8%)	53/78 (67.9%)	1.00
Vasopressors/inotropes at ICU admission	125/283 (44.2%)	73/166 (44.0%)	52/117 (44.4%)	1.00	89/208 (42.8%)	58/132 (43.9%)	31/76 (40.8%)	0.67	16/32 (50.0%)	42/100 (42.0%)	0.54
RRT at ICU admission ^b	4/203 (2.0%)	4/125 (3.2%)	0/78 (0%)	0.30	4/154 (2.6%)	4/108 (3.7%)	0/46 (0%)	0.32	1/24 (4.2%)	3/84 (3.6%)	1.00
CRP (mg/L)	159 (62 – 263) (n = 275)	117 (37 – 219) (n = 160)	215 (102 – 307) (n = 115)	< 0.0001	170 (68 – 263) (n = 204)	122 (42 – 228) (n = 128)	228 (131 – 287)	< 0.0001	186 (100 – 244) (n = 33)	89 (34 – 223) (n = 95)	0.027

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
WBC (x 10 ⁹ /L)	10.50 (5.90 – 15.69) (n = 285)	8.73 (5.06 – 14.01) (n = 168)	12.52 (8.02 – 18.08) (n = 117)	< 0.0001	10.36 (5.90 – 15.14) (n = 210)	8.40 (4.75 – 14.06) (n = 134)	12.25 (8.14 – 18.23) (n = 76)	< 0.001	6.42 (3.88 – 12.02)	10.26 (5.43 – 14.58) (n = 100)	0.09
Lymphocyte count (x 10 ⁹ /L) ^b	0.60 (0.36 – 1.14) (n = 101)	0.50 (0.33 – 1.10) (n = 55)	0.80 (0.38 – 1.40) (n = 46)	0.16	0.52 (0.32 – 1.10) (n = 86)	0.49 (0.32 – 1.10) (n = 48)	0.63 (0.30 – 1.25) (n = 38)	0.44	0.40 (0.26 – 0.60) (n = 13)	0.56 (0.35 – 1.18) (n = 35)	0.10
Haemoglobin (mmol/L)	7.45 (6.45 – 8.35) (n = 277)	7.70 (6.52 – 8.67) (n = 161)	7.14 (6.28 – 7.90) (n = 116)	0.004	7.36 (6.30 – 8.32) (n = 204)	7.70 (6.50 – 8.65) (n = 129)	7.07 (6.02 – 7.80) (n = 75)	0.002	7.73 (6.21 – 8.90) (n = 32)	7.70 (6.62 – 8.60) (n = 97)	0.93
Platelet count (x 10 ⁹ /L)	192 (134 – 257) (n = 281)	180 (126 – 241) (n = 165)	215 (144 – 305) (n = 116)	0.001	199 (132 – 258) (n = 208)	185 (126 – 242) (n = 132)	226 (149 – 339) (n = 76)	0.001	140 (94 – 240) (n = 33)	187 (132 – 244) (n = 99)	0.13
Urea (mmol/L)	12.1 (6.7 – 22.2) (n = 190)	10.7 (5.5 – 20.5) (n = 115)	13.8 (10.0 – 24.4) (n = 75)	0.002	12.1 (6.7 – 23.0) (n = 145)	10.8 (5.9 – 18.9) (n = 99)	16.8 (11.3 – 28.4) (n = 46)	< 0.001	14.7 (6.2 – 22.3) (n = 21)	10.0 (5.5 – 18.7) (n = 78)	0.19
Creatinine (μmol/L)	105 (64 – 157) (n = 278)	96 (62 – 144) (n = 166)	125 (66 – 177) (n = 112)	0.019	104 (65 – 158) (n = 207)	98 (64 – 142) (n = 133)	128 (69 – 188) (n = 74)	0.025	89 (64 – 133) (n = 33)	102 (64 – 146) (n = 100)	0.72
Estimated GFR (mL/min.)	59 (34 – 90) (n = 261)	61 (37 – 90) (n = 156)	50 (29 – 88) (n = 105)	0.08	59 (32 – 90) (n = 193)	65 (37 – 90) (n = 124)	45 (28 – 90) (n = 69)	0.049	76 (36 – 90) (n = 33)	63 (37 – 90) (n = 91)	0.96
Arterial pH	7.36 (7.25 – 7.44) (n = 281)	7.35 (7.25 – 7.44) (n = 165)	7.36 (7.25 – 7.45) (n = 116)	0.79	7.37 (7.27 – 7.45) (n = 208)	7.36 (7.26 – 7.44) (n = 133)	7.38 (7.30 – 7.46) (n = 75)	0.10	7.39 (7.25 – 7.48) (n = 32)	7.34 (7.26 – 7.42) (n = 101)	0.25
AKI present at ICU admission	84/260 (32.3%)	50/157 (31.8%)	34/103 (33.0%)	0.89	66/194 (34.0%)	43/126 (34.1%)	23/68 (33.8%)	1.00	12/30 (40.0%)	31/96 (32.3%)	0.51
AKI stage 1	48/255 (18.8%)	28/155 (18.1%)	20/100 (20.0%)	0.74	37/191 (19.4%)	24/124 (19.4%)	13/67 (19.4%)	1.00	4/29 (13.8%)	20/95 (21.1%)	0.59
AKI stage 2	10/255 (3.9%)	5/155 (3.2%)	5/100 (5.0%)	0.52	8/191 (4.2%)	5/124 (4.0%)	3/67 (4.5%)	1.00	2/29 (6.9%)	3/95 (3.2%)	0.33
AKI stage 3	21/255 (8.2%)	15/155 (9.7%)	6/100 (6.0%)	0.36	18/191 (9.4%)	12/124 (9.7%)	6/67 (9.0%)	1.00	5/29 (17.2%)	7/95 (7.4%)	0.15
Total bilirubin (μmol/L)	8.00 (5.13 – 11.99) (n = 276)	7.00 (5.00 – 10.47) (n = 162)	9.41 (5.91 – 15.67) (n = 114)	< 0.001	7.35 (5.13 – 11.97) (n = 207)	6.84 (5.00 – 10.26) (n = 131)	10.35 (6.00 – 16.21) (n = 76)	< 0.001	6.84 (5.13 – 10.05) (n = 33)	6.67 (5.00 – 10.47) (n = 98)	0.94
Direct bilirubin (μmol/L)	4.98 (3.59 – 8.93) (n = 102)	4.71 (3.25 – 9.15) (n = 52)	5.90 (3.85 – 8.68) (n = 50)	0.22	4.96 (3.42 – 8.21) (n = 85)	4.62 (3.25 – 8.55) (n = 49)	5.30 (3.59 – 8.21) (n = 36)	0.36	4.62 (3.59 – 8.89) (n = 11)	4.45 (3.08 – 7.56) (n = 38)	0.49
ALAT (IU/L)	29 (19 – 56) (n = 181)	28 (20 – 64) (n = 110)	30 (18 – 53) (n = 71)	0.60	28 (20 – 58) (n = 143)	28 (20 – 68) (n = 98)	28 (17 – 54) (n = 45)	0.51	28 (21 – 67) (n = 22)	29 (20 – 68) (n = 76)	0.57
GGT (IU/L)	52 (26 – 98) (n = 176)	56 (30 – 100) (n = 105)	36 (22 – 97) (n = 71)	0.18	54 (28 – 104) (n = 139)	56 (30 – 109) (n = 94)	33 (23 – 95) (n = 45)	0.22	83 (31 – 127) (n = 21)	54 (30 – 96) (n = 73)	0.21
Albumin (g/L)	30 (26 – 34) (n = 172)	30 (26 – 34) (n = 96)	30 (26 – 34) (n = 76)	0.95	30 (25 – 34) (n = 129)	30 (25 – 34) (n = 83)	30 (26 – 33) (n = 46)	0.78	27 (24 – 32) (n = 21)	32 (25 – 35) (n = 62)	0.06

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Ferritin (µg/L)	502 (225 – 1554) (n = 109)	568 (345 – 1974) (n = 46)	438 (195 – 1353) (n = 63)	0.10	517 (248 – 1591) (n = 103)	590 (358 – 2116) (n = 45)	457 (192 – 1430) (n = 58)	0.13	778 (334 – 2130) (n = 13)	532 (355 – 2257) (n = 32)	0.77
Triglycerides (mmol/L)	1.23 (0.84 – 1.63) (n = 127)	1.12 (0.83 – 1.71) (n = 56)	1.28 (0.92 – 1.54) (n = 71)	0.87	1.28 (0.86 – 1.68) (n = 111)	1.20 (0.85 – 1.76) (n = 53)	1.29 (0.90 – 1.59) (n = 58)	0.92	1.33 (0.76 – 1.67) (n = 17)	1.17 (0.93 – 1.81) (n = 36)	0.84
Fibrinogen (mg/L)	4895 (3363 – 7155) (n = 84)	4500 (2990 – 7000) (n = 39)	5160 (3875 – 7470) (n = 45)	0.11	4900 (3185 – 7140) (n = 73)	4380 (2920 – 7025) (n = 38)	5340 (3950 – 7170) (n = 35)	0.11	6740 (4240 – 7400) (n = 12)	3795 (2418 – 6125) (n = 26)	0.021
Microbiology at ICU admission											
Influenza – Influenza A	147/292 (50.3%)	147/174 (84.5%)	0/118 (0%)	NA	124/216 (57.4%)	124/140 (88.6%)	0/76 (0%)	NA	32/34 (94.1%)	92/106 (86.8%)	0.36
Influenza – Influenza B	27/292 (9.2%)	27/174 (15.5%)	0/118 (0%)	NA	16/216 (7.4%)	16/140 (11.4%)	0/76 (0%)	NA	2/34 (5.9%)	14/106 (13.2%)	0.36
Influenza – Negative	118/292 (40.4%)	0/174 (0%)	118/118 (100%)	NA	76/216 (35.2%)	0/140 (0%)	76/76 (100%)	NA	NA	NA	NA
Influenza subtype – H1N1	NA	23/147 (15.6%)	NA	NA	NA	16/124 (12.9%)	NA	NA	2/32 (6.3%)	14/92 (15.2%)	0.06 ^c
Influenza subtype – H3N2	NA	11/147 (7.5%)	NA	NA	NA	9/124 (7.3%)	NA	NA	0/32 (0%)	9/92 (9.8%)	
Influenza subtype – Unknown/pending	NA	113/147 (76.9%)	NA	NA	NA	99/124 (79.8%)	NA	NA	30/32 (93.8%)	69/92 (75.0%)	
Days between ICU admission and positive influenza test	NA	0 (-1 – 0) (n = 174)	NA	NA	NA	0 (-1 – 0)	NA	NA	0 (-1 – 1)	0 (-1 – 0)	0.74
Bacterial cultures/PCR performed on respiratory material < 7 days of influenza or niCAP diagnosis	253/264 (95.8%)	139/146 (95.2%)	114/118 (96.6%)	0.76	186/194 (95.9%)	113/118 (95.8%)	73/76 (96.1%)	1.00	30/30 (100%)	83/88 (94.3%)	0.33
Bacterial lung pathogens cultured/PCR positive from respiratory sample < 7 days of influenza or niCAP diagnosis	106/253 (41.9%)	50/139 (36.0%)	56/114 (49.1%)	0.041	72/186 (38.7%)	40/113 (35.4%)	32/73 (43.8%)	0.28	12/30 (40.0%)	28/83 (33.7%)	0.66
Pneumococcal urinary antigen test performed at time of influenza or niCAP diagnosis	78/248 (31.5%)	45/136 (33.1%)	33/112 (29.5%)	0.58	47/180 (26.1%)	37/109 (33.9%)	10/71 (14.1%)	0.003	6/26 (23.1%)	31/83 (37.3%)	0.24
<i>Legionella</i> urinary antigen test performed at time of influenza or niCAP diagnosis	138/248 (55.6%)	62/136 (45.6%)	76/112 (67.9%)	< 0.001	103/180 (57.2%)	54/109 (49.5%)	49/71 (69.0%)	0.013	13/26 (50.0%)	41/83 (49.4%)	1.00

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Positive urinary antigen test – <i>S. pneumoniae</i>	12/78 (15.4%)	6/45 (13.3%)	6/33 (18.2%)	0.75	7/47 (14.9%)	6/37 (16.2%)	1/10 (10.0%)	1.00	1/6 (16.7%)	5/31 (16.1%)	1.00
Positive urinary antigen test – <i>Legionella</i>	6/138 (4.3%)	0/62 (0%)	6/76 (7.9%)	0.033	2/103 (1.9%)	0/54 (0%)	2/49 (4.1%)	0.22	0/13 (0%)	0/41 (0%)	NA
<i>Aspergillus</i> cultures performed on respiratory material at the time of influenza or niCAP diagnosis ^d	183/256 (71.5%)	102/141 (72.3%)	81/115 (70.4%)	0.78	143/187 (76.5%)	83/113 (73.5%)	60/74 (81.1%)	0.29	21/28 (75.0%)	62/85 (72.9%)	1.00
<i>Aspergillus</i> cultured from respiratory sample at time of influenza or niCAP diagnosis ^d	9/183 (4.9%)	9/102 (8.8%)	0/81 (0%)	0.005	8/143 (5.6%)	8/83 (9.6%)	0/60 (0%)	0.021	6/21 (28.6%)	2/62 (3.2%)	0.003
PJ PCR performed on respiratory material < 7 days of influenza or niCAP diagnosis	186/262 (71.0%)	103/145 (71.0%)	83/117 (70.9%)	1.00	145/192 (75.5%)	85/117 (72.6%)	60/75 (80.0%)	0.30	26/30 (86.7%)	59/87 (67.8%)	0.06
PJ PCR positive on respiratory sample < 7 days of influenza or niCAP diagnosis	17/186 (9.1%)	5/103 (4.9%)	12/83 (14.5%)	0.038	13/145 (9.0%)	3/85 (3.5%)	10/60 (16.7%)	0.008	2/26 (7.7%)	1/59 (1.7%)	0.22
Other viral testing performed on respiratory material < 7 days of influenza or niCAP diagnosis	240/265 (90.6%)	135/147 (91.8%)	105/118 (89.0%)	0.53	174/194 (89.7%)	106/118 (89.8%)	68/76 (89.5%)	1.00	28/30 (93.3%)	78/88 (88.6%)	0.73
Other viral testing positive on respiratory sample < 7 days of influenza or niCAP diagnosis	87/240 (36.3%)	34/135 (25.2%)	53/105 (50.5%)	< 0.0001	68/174 (39.1%)	29/106 (27.4%)	39/68 (57.4%)	< 0.001	15/28 (53.6%)	14/78 (17.9%)	< 0.001
Treatment at the time of ICU admission											
SDD or SOD started at admission to study site ICU	200/284 (70.4%)	116/170 (68.2%)	84/114 (73.7%)	0.35	153/216 (70.8%)	96/140 (68.6%)	57/76 (75.0%)	0.35	25/34 (73.5%)	71/106 (67.0%)	0.53
Influenza treatment – Oseltamivir	NA	151/174 (86.8%)	NA	NA	NA	124/140 (88.6%)	NA	NA	29/34 (85.3%)	95/106 (89.6%)	0.54
Influenza treatment – No influenza treatment	NA	23/174 (13.2%)	NA	NA	NA	16/140 (11.4%)	NA	NA	5/34 (14.7%)	11/106 (10.4%)	0.54
Systemic antifungal treatment at the time of ICU admission	11/288 (3.8%)	6/172 (3.5%)	5/116 (4.3%)	0.76	9/215 (4.2%)	6/139 (4.3%)	3/76 (3.9%)	1.00	2/34 (5.9%)	4/105 (3.8%)	0.63
Fluconazole	5/288 (1.7%)	1/172 (0.6%)	4/116 (3.4%)	0.16	3/215 (1.4%)	1/139 (0.7%)	2/76 (2.6%)	0.29	0/34 (0%)	1/105 (1.0%)	1.00

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Voriconazole	6/288 (2.1%)	5/172 (2.9%) ^{ef}	1/116 (0.9%)	0.41	6/215 (2.8%)	5/139 (3.6%) ^{ef}	1/76 (1.3%)	0.43	2/34 (5.9%) ^e	3/105 (2.9%) ^f	0.60
Anidulafungin	1/288 (0.3%)	1/172 (0.6%) ^e	0/116 (0%)	1.00	1/215 (0.5%)	1/139 (0.7%) ^e	0/76 (0%)	1.00	1/34 (2.9%) ^e	0/105 (0%)	0.24
Caspofungin	2/288 (0.7%)	2/172 (1.2%) ^{ef}	0/116 (0%)	0.52	2/215 (0.9%)	2/139 (1.4%) ^{ef}	0/76 (0%)	0.54	1/34 (2.9%) ^e	1/105 (1.0%) ^f	0.43
Liposomal amphotericin B	1/288 (0.3%)	1/172 (0.6%) ^f	0/116 (0%)	1.00	1/215 (0.5%)	1/139 (0.7%) ^f	0/76 (0%)	1.00	0/34 (0%)	1/105 (1.0%) ^f	1.00
Systemic antifungals continued at ICU admission	7/11 (63.6%)	3/6 (50.0%)	4/5 (80.0%)	1.00 ^c	5/9 (55.6%)	3/6 (50.0%)	2/3 (66.7%)	1.00 ^c	1/2 (50.0%)	2/4 (50.0%)	0.60 ^c
Systemic antifungals switched at ICU admission	1/11 (9.1%)	1/6 (16.7%) ^e	0/5 (0%)		1/9 (11.1%)	1/6 (16.7%) ^e	0/3 (0%)		1/2 (50.0%) ^e	0/4 (0%)	
Systemic antifungal treatment stopped at ICU admission	3/11 (27.3%)	2/6 (33.3%) ^f	1/5 (20.0%)		3/9 (33.3%)	2/6 (33.3%) ^f	1/3 (33.3%)		0/2 (0%)	2/4 (50.0%) ^f	
On <i>Aspergillus</i> -active antifungal treatment at the time of ICU admission	6/288 (2.1%)	5/172 (2.9%)	1/116 (0.9%)	0.41	6/215 (2.8%)	5/139 (3.6%)	1/76 (1.3%)	0.43	2/34 (5.9%)	3/105 (2.9%)	0.60
<i>Aspergillus</i> -active antifungal treatment continued at the time of ICU admission	4/288 (1.4%)	3/172 (1.7%)	1/116 (0.9%)	0.65	4/215 (1.9%)	3/139 (2.2%)	1/76 (1.3%)	1.00	2/34 (5.9%)	1/105 (1.0%)	0.15
Diagnostic mycological testing performed											
Bronchoscopy performed	131/261 (50.2%)	88/156 (56.4%)	43/105 (41.0%)	0.017	126/211 (59.7%)	83/136 (61.0%)	43/75 (57.3%)	0.66	34/34 (100%)	49/102 (48.0%)	NA
BAL performed	138/266 (51.9%)	90/161 (55.9%)	48/105 (45.7%)	0.13	133/215 (61.9%)	85/140 (60.7%)	48/75 (64.0%)	0.66	34/34 (100%)	51/106 (48.1%)	NA
BALF GM performed	132/265 (49.8%)	88/160 (55.0%)	44/105 (41.9%)	0.045	128/215 (59.5%)	84/140 (60.0%)	44/75 (58.7%)	0.88	34/34 (100%)	50/106 (47.2%)	NA
BALF culture performed	120/261 (46.0%)	80/156 (51.3%)	40/105 (38.1%)	0.043	116/211 (55.0%)	76/136 (55.9%)	40/75 (53.3%)	0.77	31/33 (93.9%)	45/103 (43.7%)	NA
Serum GM performed	162/263 (61.6%)	103/159 (64.8%)	59/104 (56.7%)	0.20	159/214 (74.3%)	100/140 (71.4%)	59/74 (79.7%)	0.25	29/34 (85.3%)	71/106 (67.0%)	NA
TBA fungal culture performed	65/251 (25.9%)	60/147 (40.8%)	5/104 (4.8%)	< 0.0001	54/204 (26.5%)	52/130 (40.0%)	2/74 (2.7%)	< 0.0001	18/32 (56.3%)	34/98 (34.7%)	NA
Sputum fungal culture performed	146/256 (57.0%)	91/152 (59.9%)	55/104 (52.9%)	0.30	124/208 (59.6%)	83/134 (61.9%)	41/74 (55.4%)	0.38	16/32 (50.0%)	67/102 (65.7%)	NA

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
ICU treatment data											
Ventilatory support at any time during ICU admission	255/286 (89.2%)	150/170 (88.2%)	105/116 (90.5%)	0.57	194/211 (91.9%)	125/136 (91.9%)	69/75 (92.0%)	1.00	34/34 (100%)	91/102 (89.2%)	0.06
Non-invasive ventilatory support at any time during ICU admission	122/214 (57.0%)	67/130 (51.5%)	55/84 (65.5%)	0.049	97/155 (62.6%)	59/106 (55.7%)	38/49 (77.6%)	0.012	14/24 (58.3%)	45/82 (54.9%)	0.82
Invasive ventilatory support at any time during ICU admission	132/229 (57.6%)	87/142 (61.3%)	45/87 (51.7%)	0.17	102/168 (60.7%)	76/117 (65.0%)	26/51 (51.0%)	0.12	26/29 (89.7%)	50/88 (56.8%)	0.001
Prone ventilation at any time during ICU admission	54/286 (18.9%)	39/170 (22.9%)	15/116 (12.9%)	0.045	42/211 (19.9%)	35/136 (25.7%)	7/75 (9.3%)	0.004	15/34 (44.1%)	20/102 (19.6%)	0.007
Inhaled NO ventilation	14/214 (6.5%)	6/130 (4.6%)	8/84 (9.5%)	0.17	12/155 (7.7%)	6/106 (5.7%)	6/49 (12.2%)	0.20	3/24 (12.5%)	3/82 (3.7%)	0.13
ECMO / ECCO ₂ R	25/286 (8.7%)	19/170 (11.2%)	6/116 (5.2%)	0.09	20/211 (9.5%)	17/136 (12.5%)	3/75 (4.0%)	0.050	8/34 (23.5%)	9/102 (8.8%)	0.036
Vasopressors/inotropes at any time during ICU admission	174/243 (71.6%)	104/144 (72.2%)	70/99 (70.7%)	0.88	126/181 (69.6%)	86/120 (71.7%)	40/61 (65.6%)	0.40	25/29 (86.2%)	61/91 (67.0%)	0.06
AKI at any time during ICU admission	121/263 (46.0%)	75/157 (47.8%)	46/106 (43.4%)	0.53	95/198 (48.0%)	65/128 (50.8%)	30/70 (42.9%)	0.30	21/33 (63.6%)	44/95 (46.3%)	0.11
Highest AKI stage 1	32/109 (29.4%)	13/68 (19.1%)	19/41 (46.3%)	0.004	25/87 (28.7%)	12/59 (20.3%)	13/28 (46.4%)	0.021	0/19 (0%)	12/40 (30.0%)	0.006
Highest AKI stage 2	21/109 (19.3%)	14/68 (20.6%)	7/41 (17.1%)	0.80	15/87 (17.2%)	11/59 (18.6%)	4/28 (14.3%)	0.77	2/19 (10.5%)	9/40 (22.5%)	0.48
Highest AKI stage 3	56/109 (51.4%)	41/68 (60.3%)	15/41 (36.6%)	0.019	47/87 (54.0%)	36/59 (61.0%)	11/28 (39.3%)	0.07	17/19 (89.5%)	19/40 (47.5%)	0.002
RRT at any time during ICU admission	42/285 (14.7%)	31/169 (18.3%)	11/116 (9.5%)	0.042	36/211 (17.1%)	28/136 (20.6%)	8/75 (10.7%)	0.09	15/33 (45.5%)	13/103 (12.6%)	< 0.001
Any systemic corticosteroids during ICU admission	176/291 (60.5%)	107/173 (61.8%)	69/118 (58.5%)	0.63	141/216 (65.3%)	91/140 (65.0%)	50/76 (65.8%)	1.00	24/34 (70.6%)	67/106 (63.2%)	0.54
Median cumulative corticosteroid dose during ICU admission, mg/kg prednisone equivalent	3.31 (1.35 – 9.42) (n = 176)	3.39 (1.44 – 12.07) (n = 107)	3.13 (1.04 – 8.90) (n = 69)	0.33	3.39 (1.39 – 10.83) (n = 141)	3.21 (1.34 – 11.96) (n = 91)	3.58 (1.39 – 9.50) (n = 50)	0.92	4.55 (1.38 – 12.04) (n = 24)	2.57 (1.34 – 10.31) (n = 67)	0.32
Any systemic antifungal treatment during ICU admission	68/291 (23.4%)	54/173 (31.2%)	14/118 (11.9%)	< 0.001	60/216 (27.8%)	49/140 (35.0%)	11/76 (14.5%)	0.001	29/34 (85.3%)	20/106 (18.9%)	< 0.0001

	Total population (n = 292)	Influenza (n = 174)	Severe niCAP (n = 118)	p value (influenza vs. niCAP)	Total classifiable population (n = 216)	Classifiable influenza (n = 140)	Classifiable severe niCAP (n = 76)	p value (classifiable influenza vs. niCAP)	IAPA (n = 34)	No IAPA (n = 106)	p value (IAPA versus no IAPA)
Outcome data											
IAPA/IPA	44/216 (20.4%)	34/140 (24.3%)	10/76 (13.2%)	0.054	44/216 (20.4%)	34/140 (24.3%)	10/76 (13.2%)	0.054	NA	NA	NA
ICU Mortality	57/292 (19.5%)	38/174 (21.8%)	19/118 (16.1%)	0.23	43/216 (19.9%)	30/140 (21.4%)	13/76 (17.1%)	0.48	15/34 (44.1%)	15/106 (14.2%)	< 0.001
ICU Mortality if BAL performed at any time during ICU admission									15/34 (44.1%)	11/51 (21.6%)	0.033
LOS ICU (days)	7 (4 – 18) (n = 276)	8 (3 – 21) (n = 164)	7 (4 – 13) (n = 112)	0.17	9 (4 – 20) (n = 206)	9 (4 – 22) (n = 131)	8 (4 – 15) (n = 75)	0.39	21 (9 – 45) (n = 33)	7 (3 – 18) (n = 98)	< 0.0001
LOS Hospital (days)	15 (10 – 32) (n = 249)	17 (10 – 36) (n = 148)	14 (9 – 25) (n = 101)	0.06	17 (10 – 34) (n = 183)	20 (10 – 37) (n = 118)	14 (11 – 26) (n = 65)	0.13	27 (16 – 48) (n = 29)	16 (10 – 35) (n = 89)	0.012
LOS ICU (days) – Alive at ICU discharge	6 (3 – 15) (n = 219)	6 (3 – 17) (n = 126)	7 (3 – 13) (n = 93)	1.00	7 (3 – 16) (n = 163)	6 (3 – 19) (n = 101)	7 (4 – 14) (n = 62)	0.85	29 (5 – 51) (n = 18)	6 (3 – 13) (n = 83)	0.002
LOS Hospital (days) – Alive at ICU discharge	15 (10 – 31) (n = 193)	15 (10 – 35) (n = 111)	15 (10 – 28) (n = 82)	0.75	16 (10 – 34) (n = 141)	18 (10 – 37) (n = 89)	16 (10 – 29) (n = 52)	0.75	39 (14 – 69) (n = 14)	15 (8 – 34) (n = 75)	0.014

Data are presented as median (IQR) or as proportions (percentages).

a = Prolonged use of corticosteroids defined according to EORTC/MSGERC guidelines as a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for > 3 weeks and excluding patients with allergic bronchopulmonary aspergillosis.

b = Data not available for 2017/2018 cohort.

c = Fisher-Freeman-Halton exact test

d = Data not available for patients in the POSA FLU database (n = 26).

e = In one patient, voriconazole + anidulafungin + caspofungin was switched to voriconazole + caspofungin after admission to ICU

f = In one patient, voriconazole + caspofungin + liposomal amphotericin B were stopped after admission to ICU. In another patient, voriconazole monotherapy was stopped after admission to ICU.

AID = Auto-immune disease. AIDS = Acquired immunodeficiency syndrome. AKI = Acute kidney injury. ALAT = Alanine aminotransferase. APACHE = Acute physiology and chronic health evaluation. BAL = Bronchoalveolar lavage. BALF = Bronchoalveolar lavage fluid. BMI = Body mass index. BSA = Body surface area. CKD = Chronic kidney disease. COPD = Chronic obstructive pulmonary disease. CRP = C reactive protein. ECCO₂R = Extracorporeal carbon dioxide removal. ECMO = Extracorporeal membrane oxygenation. EORTC/MSGERC = European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium. GFR = Glomerular filtration rate. GGT = Gamma-glutamyl transferase. GM = Galactomannan. HIV = Human immunodeficiency virus. IAPA = Influenza-associated pulmonary aspergillosis. ICU = Intensive care unit. ILD = Interstitial lung disease. LOS = Length of stay. MAP = Mean arterial pressure. NA = Not applicable. niCAP = Non-influenza community-acquired pneumonia. NO = Nitric oxide. PCR = Polymerase chain reaction. PJ = *Pneumocystis jirovecii*. RRT = Renal replacement therapy. SCT = Stem cell transplantation. SDD = Selective digestive tract decontamination. SOD = Selective oropharyngeal decontamination. TB = Tuberculosis. TBA = Tracheobronchial aspirate. WBC = White blood cell count.

Supplementary Table 2. Additional clinical information on patients with IAPA or IPA

Classification	Influenza /niCAP	Demographics	PMH	EORTC host factors	Invasive ventilatory support	Serum GM (highest ODI)	BALF GM (highest ODI)	BALF Culture	TBA Culture	Sputum Culture	Days between ICU admission and first positive mycological criterion (and which test)	Radiology	Initial antifungal treatment	ICU LOS (days) and outcome	Other remarks
Proven IAPA	Influenza	66, M	CVD, DM	-	Y (prone)	-	-	-	NP	NP	NA	Infiltrates	NA	9, Death	Autopsy: Necrotising <i>Aspergillus</i> pneumonia in right lower lobe and focus of <i>Aspergillus</i> in myocardium
Proven IAPA	Influenza	51, M	Nil	-	Y (prone)	-	+ (2.1)	+ (<i>A. fumigatus</i>)	-	+ (<i>A. fumigatus</i>)	4 (BALF GM + BALF culture)	Infiltrates	Voriconazole + anidulafungin	33, Death	Autopsy: Bilateral viral pneumonia influenza with fungal infection
Probable IAPA	Influenza	66, M	Metastased melanoma	+ (CS, cytotoxic)	U	-	+ (5.4)	-	-	-	3 (BALF GM)	Infiltrates	Voriconazole	9, Death	
Probable IAPA	Influenza	63, M	Lung Tx, CVD, DM, other	+ (SOT, TB IS)	U	-	+ (5.0)	+ (<i>A. fumigatus</i>)	NP	-	5 (BALF GM + BALF culture)	Infiltrates	Voriconazole	12, Alive	
Probable ITBA/IAPA	Influenza	47, M	Liver cirrhosis	-	Y (prone, ECMO)	-	+ (5.3)	-	NP	-	15 (BALF GM)	Infiltrates	Voriconazole	40, Death	
Probable IAPA	Influenza	63, F	Congenital immunodeficiency syndrome	+ (inherited IDS)	Y (prone)	-	+ (5.4)	-	NP	NP	6 (BALF GM)	Infiltrates	Voriconazole	50, Alive	
Probable IAPA	Influenza	45, F	Other	-	U	-	+ (1.9)	-	NP	-	0 (BALF GM)	Infiltrates	Nil	2, Alive	
Probable IAPA	Influenza	62, F	CLL, other (monoclonal B cell lymphocytosis)	-	U	-	+ (5.5)	-	NP	NP	0 (BALF GM)	Infiltrates	Voriconazole	6, Alive	
Probable IAPA	Influenza	68, F	Lung Tx, CVD, COPD, other	+ (SOT, TB IS)	U	-	+ (2.1)	-	NP	NP	1 (BALF GM)	Infiltrates	Voriconazole	29, Alive	
Probable ITBA/IAPA	Influenza	54, M	CVD, CKD requiring RRT	-	Y (prone, ECMO)	+ (1.3)	+ (5.8)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	-	3 (BALF GM)	Infiltrates	Voriconazole	69, Alive	

Classification	Influenza /niCAP	Demographics	PMH	EORTC host factors	Invasive ventilatory support	Serum GM (highest ODI)	BALF GM (highest ODI)	BALF Culture	TBA Culture	Sputum Culture	Days between ICU admission and first positive mycological criterion (and which test)	Radiology	Initial antifungal treatment	ICU LOS (days) and outcome	Other remarks
Probable IAPA	Influenza	36, M	Nil	-	Y (prone, ECMO)	-	+ (1.4)	+ (<i>A. fumigatus</i>)	U	U	1 (BALF GM + BALF culture)	Unknown → Infiltrates	Voriconazole	17, Death	
Probable ITBA	Influenza	68, F	Nil	-	Y	NP	+ (6.56)	U	U	U	1 (BALF GM)	Unknown	Voriconazole	49, Alive	
Probable IAPA	Influenza	85, M	CVD, CKD not requiring RRT, other	-	N	-	+ (1.3)	NP	NP	NP	1 (BALF GM)	Infiltrates	Voriconazole	3, Alive	
Probable IAPA	Influenza	68, M	CVD, DM, COPD, bladder carcinoma, lung carcinoma, other	-	Y (NO)	-	+ (4.0)	-	+ (<i>A. fumigatus</i>)	NP	17 (BALF GM)	Infiltrates	Voriconazole	29, Death	
Probable IAPA	Influenza	57, F	CVD, COPD	+ (CS)	Y (prone)	-	+ (2.2)	-	NP	NP	12 (BALF GM)	Infiltrates	Voriconazole	17, Alive	
Probable IAPA	Influenza	72, F	COPD	-	Y	-	+ (5.6)	+ (<i>A. fumigatus</i>)	NP	NP	9 (BALF GM + BALF culture)	Infiltrates	Voriconazole	17, Death	
Probable IAPA	Influenza	65, F	CVD, COPD, other	-	Y	-	+ (5.8)	-	+ (<i>A. fumigatus</i>)	-	11 (BALF GM + TBA culture)	Infiltrates	Voriconazole	42, Alive	
Probable IAPA	Influenza	61, M	Neuroendocrine gland malignancy	-	Y	NP	+ (1.3)	-	NP	NP	33 (BALF GM)	Infiltrates	Nil	34, Death	
Probable IAPA	Influenza	26, M	SCT > 90 days prior to admission, Hodgkin lymphoma	+ (alloSCT, CS, acquired ID, cytotoxic)	Y (ECMO)	+ (0.6)	+ (1.3)	-	+ (<i>A. fumigatus</i>)	NP	8 (BALF GM + TBA culture)	Infiltrates	Liposomal amphotericin B	61, Death	
Probable IAPA	Influenza	72, M	CVD, other malignancy	-	Y (NO, ECMO)	-	-	+ (<i>A. niger</i>)	NP	NP	4 (BALF culture)	Infiltrates	Nil	14, Death	
Probable IAPA	Influenza	67, F	CVD, other	-	Y	-	+ (1.9)	-	NP	NP	0 (BALF GM)	Infiltrates	Voriconazole	7, Alive	
Probable IAPA	Influenza	66, F	Acute leukaemia < 90 days prior to	-	Y (prone, NO)	-	+ (1.9)	+ (Unknown)	-	NP	13 (BALF culture)	Infiltrates	Caspofungin	54, Alive	

Classification	Influenza /niCAP	Demographics	PMH	EORTC host factors	Invasive ventilatory support	Serum GM (highest ODI)	BALF GM (highest ODI)	BALF Culture	TBA Culture	Sputum Culture	Days between ICU admission and first positive mycological criterion (and which test)	Radiology	Initial antifungal treatment	ICU LOS (days) and outcome	Other remarks
			admission, CVD, COPD, tubulovillous polyp with carcinoma in situ, other												
Probable IAPA	Influenza	63, M	DM, COPD	-	Y (prone)	-	-	+ (<i>A. fumigatus</i>)	-	-	3 (BALF culture)	Infiltrates	Voriconazole + anidulafungin	65, Alive	
Probable IAPA	Influenza	61, M	Nil	-	Y	-	+ (1.1)	NP	-	-	19 (BALF GM)	Infiltrates	Voriconazole + liposomal amphotericin B	U, Alive	Patient transferred to another hospital; still on ventilatory support at the time of transfer
Probable IAPA	Influenza	69, M	CVD, other	-	Y (ECMO)	NP	-	+ (<i>A. fumigatus</i>)	-	-	6 (BALF culture)	Infiltrates	Voriconazole + caspofungin	19, Death	
Probable IAPA	Influenza	38, F	AID, psoriasis, other	+ (TB IS)	Y (prone, ECMO)	+ (1.3)	+ (5.0)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	3 (Serum GM + Sputum culture)	Infiltrates	Anidulafungin	28, Alive	
Probable IAPA	Influenza	67, M	Multiple myeloma, other (monoclonal gammopathy of unknown significance)	+ (TB IS, cytotoxic)	N	-	-	+ (<i>A. fumigatus</i>)	NP	NP	5 (BALF culture)	Infiltrates	Voriconazole	3, Alive	BAL performed 2 days after ICU discharge (temporary readmission to ICU): positive culture, negative GM
Probable IAPA	Influenza	68, M	Nil	U	Y (prone)	NP	-	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	27 (BALF culture)	Infiltrates	Voriconazole	47, Death	
Probable ITBA/IAPA	Influenza	68, M	CVD	U	Y (prone)	-	+ (6.9)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i>)	4 (BALF GM + BALF culture)	Infiltrates + cavitating infiltrates	Voriconazole + anidulafungin	85, Alive	

Classification	Influenza /niCAP	Demographics	PMH	EORTC host factors	Invasive ventilatory support	Serum GM (highest ODI)	BALF GM (highest ODI)	BALF Culture	TBA Culture	Sputum Culture	Days between ICU admission and first positive mycological criterion (and which test)	Radiology	Initial antifungal treatment	ICU LOS (days) and outcome	Other remarks
Probable IAPA	Influenza	64, M	Multiple myeloma	+ (alloSCT, CS, cytotoxic)	Y (prone)	NP	+ (1.0)	+ (<i>A. fumigatus</i>)	-	-	0 (BALF GM)	Infiltrates	Anidulafungin	21, Death	
Probable IAPA	Influenza	49, M	COPD	-	Y	-	-	+ (Unknown)	-	-	3 (BALF culture)	Infiltrates	Nil	34, Alive	
Probable IAPA	Influenza	69, F	CVD, DM, COPD	-	Y (prone, ECMO)	+ (1.1)	+ (2.9)	+ (<i>A. fumigatus</i>)	+ (<i>A. fumigatus</i> , later <i>A. terreus</i>)	-	1 (BALF GM + BALF culture)	Infiltrates + cavitating infiltrates	Voriconazole	12, Death	
Probable IAPA	Influenza	85, M	Other	-	N	-	+ (1.3)	-	-	NP	1 (BALF GM)	Infiltrates	Voriconazole	3, Alive	
Probable ITBA/IAPA	Influenza	63, M	Other	-	Y (prone)	+ (3.5)	+ (8.9)	+ (<i>A. fumigatus</i>)	-	NP	2 (Serum GM + BALF GM + BALF culture)	Infiltrates	Voriconazole + micafungin	4, Death	
Probable IPA	niCAP	75, F	Kidney Tx, other	+ (SOT, TB IS)	N	-	+ (2.9)	-	NP	NP	1 (BALF GM)	Infiltrates	Nil	3, Alive	
Probable IPA	niCAP	80, M	CVD, asthma, COPD, pulmonary TB, other	-	U	-	+ (1.5)	-	NP	-	8 (BALF GM)	Infiltrates	Liposomal amphotericin B	36, Death	
Probable IPA	niCAP	51, M	Glioblastoma, other (Steinert disease, Gerstmann syndrome)	-	N	+ (3.9)	+ (5.5)	-	NP	-	1 (Serum GM)	Infiltrates	Voriconazole	18, Alive	
Probable IPA	niCAP	53, F	CVD, UC	+ (CS, TB IS)	Y (prone)	+ (0.6)	-	-	NP	NP	5 (Serum GM)	Infiltrates	Voriconazole	92, Alive	
Probable IPA	niCAP	74, M	SCT > 90 days prior to admission, MDS, cGvHD, DM, CKD not requiring RRT, other	+ (alloSCT, acquired ID)	N	-	+ (4.8)	-	NP	-	0 (BALF GM)	Infiltrates	Voriconazole	6, Alive	

Classification	Influenza/niCAP	Demographics	PMH	EORTC host factors	Invasive ventilatory support	Serum GM (highest ODI)	BALF GM (highest ODI)	BALF Culture	TBA Culture	Sputum Culture	Days between ICU admission and first positive mycological criterion (and which test)	Radiology	Initial antifungal treatment	ICU LOS (days) and outcome	Other remarks
Probable IPA	niCAP	71, F	Tonsillar carcinoma, other	-	Y (NO)	+ (1.0)	+ (4.7)	-	NP	-	0 (Serum GM)	Infiltrates	Voriconazole	24, Alive	
Probable IPA	niCAP	42, M	Nil	-	Y	-	+ (4.6)	NP	NP	NP	1 (BALF GM)	Infiltrates	Nil	5, Alive	
Probable IPA	niCAP	64, M	CVD, DM, other	-	Y (NO, ECMO)	+ (1.4)	-	-	NP	NP	2 (Serum GM)	Infiltrates	Voriconazole	32, Alive	
Probable IPA	niCAP	63, M	Lung carcinoma	-	N	-	+ (2.5)	-	NP	NP	0 (BALF GM)	Infiltrates	Nil	8, Alive	
Probable IPA	niCAP	66, M	AID	+ (TB IS)	Y	-	+ (2.42)	NP	-	-	-1 (BALF GM)	Infiltrates	Voriconazole + liposomal amphotericin B	16, Alive	

+ = Positive. - = Negative. NP = Not performed. NA = Not applicable.

Probable IAPA/IPA is defined according to the expert opinion case definition published in 2020.

AlloSCT = Allogeneic stem cell transplantation. AID = Auto-immune disease. BAL = Bronchoalveolar lavage. BALF = Bronchoalveolar lavage fluid. CD = Crohn's disease. CLL = Chronic lymphocytic leukaemia. COPD = Chronic obstructive pulmonary disease. CKD = Chronic kidney disease. CS = Corticosteroid use. CT = Computed tomography. CVD = Cardiovascular disease. Cytotox = Cytotoxic medication use. DM = Diabetes mellitus. ECMO = Extracorporeal membrane oxygenation or extracorporeal carbon dioxide removal. EORTC/MSGERC = European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium. GM = Galactomannan. ICU = Intensive care unit. ID = Immunodeficiency. IDS = Immunodeficiency syndrome. ITBA = Invasive tracheobronchial aspergillosis. ODI = Optical density index. N = No. niCAP = Non-influenza community-acquired pneumonia. NO = Inhaled nitric oxide ventilation. PJP = *Pneumocystis jirovecii* pneumonia. PMH = Past medical history. Prone = Invasive ventilation in the prone position. SCT = Stem cell transplantation. SOT = Solid organ transplantation. RRT = Renal replacement therapy. TB = Tuberculosis. TBA = Tracheobronchial aspirate. TB IS = T and/or B cell immunosuppressant use. Tx = Transplantation. UC = Ulcerative colitis. Y = Yes.

Supplementary Table 3. Time to first positive mycological test data in the classifiable influenza and severe niCAP cohort

Days between ICU admission and first positive:	Total population (n = 292)	Influenza – IAPA (n = 34)	Influenza – No IAPA (n = 106)	Severe niCAP – IPA (n = 10)	Severe niCAP – No IPA (n = 66)	p value (IAPA vs. IPA)
Serum GM	3 (1 – 7) (n = 10)	6 (3 – 10) (n = 5)	NA	2 (0 – 4) (n = 4)	NA	0.06
BALF GM	3 (1 – 9) (n = 36)	4 (1 – 11) (n = 27)	NA	1 (0 – 4) (n = 8)	NA	0.06
BALF culture	4 (1 – 8) (n = 20)	4 (3 – 9) (n = 17)	NA	NA	NA	NA
TBA culture	11 (6 – 14) (n = 13)	12 (7 – 19) (n = 8)	9 (5 – ...) (n = 2)	NA	NA	NA
Sputum culture	8 (2 – 11) (n = 10)	13 (5 – 20) (n = 4)	2 (0 – 9) (n = 5)	NA	NA	NA
Mycological criterion for ITBA and cavitary IAPA (including PR data)	3 (0 – 8) (n = 56)	4 (1 – 9) (n = 33)	5 (0 – 9) (n = 7)	1 (0 – 3)	NA	0.015
Mycological criterion for non-cavitary IAPA	3 (1 – 6) (n = 48)	4 (1 – 10) (n = 33)	NA	1 (0 – 3)	NA	0.015

Data are presented as median (IQR) and represent number of days between initial ICU admission and first positive test result of the modality reported.

BALF = Bronchoalveolar lavage fluid. GM = Galactomannan. IAPA = Influenza-associated aspergillosis. IPA = Invasive pulmonary aspergillosis. ICU = Intensive care unit. ITBA = Invasive tracheobronchial aspergillosis. NA = Not applicable. niCAP = Non-influenza community-acquired pneumonia. PR = Physician reported (as reported directly in the electronic case report form). TBA = Tracheobronchial aspirate.

Supplementary Table 4. Characteristics of patients with IAPA, survivors versus non-survivors of ICU admission

	Total IAPA population (n = 34)	Survivors (n = 19)	Non-survivors (n = 15)	p value (survivors versus non-survivors)
Median age (years)	65 (56 – 68)	63 (57 – 68)	66 (51 – 69)	0.78
Male sex	22/34 (64.7%)	9/19 (47.4%)	13/15 (86.7%)	0.030
BMI (kg/m ²)	25.7 (22.7 – 29.4)	26.2 (23.4 – 30.0)	24.8 (21.7 – 27.8)	0.29
Influenza vaccination (season of ICU admission)	3/15 (20.0%)	2/8 (25.0%)	1/7 (14.3%)	1.00
Smoking history	18/26 (69.2%)	11/18 (61.1%)	7/8 (87.5%)	0.36
Days between hospital admission and ICU admission	1 (0 – 4)	2 (1 – 3)	1 (0 – 5)	0.78
Days of illness before hospital admission	7 (3 – 9) (n = 32)	7 (4 – 9) (n = 18)	5 (3 – 8) (n = 14)	0.38
Days of illness before ICU admission	9 (6 – 14) (n = 32)	9 (6 – 11) (n = 18)	7 (6 – 15) (n = 14)	0.93
Any EORTC host factor	9/32 (28.1%)	6/18 (33.3%)	3/14 (21.4%)	0.69
APACHE II score	21 (15 – 29) (n = 17)	21 (13 – 31) (n = 12)	21 (18 – 26) (n = 5)	0.88
Ventilatory support at time of ICU admission ^a	17/24 (70.8%)	10/13 (76.9%)	7/11 (63.6%)	0.66
Vasopressors/inotropes at ICU admission	16/32 (50.0%)	9/19 (47.4%)	7/13 (53.8%)	1.00
AKI present at ICU admission	12/30 (40.0%)	7/16 (43.8%)	5/14 (35.7%)	0.72
RRT at ICU admission ^a	1/24 (4.2%)	0/13 (0%)	1/11 (9.1%)	0.46
CRP (mg/L)	186 (100 – 244) (n = 33)	176 (103 – 234) (n = 18)	195 (86 – 245)	0.84
WBC (x 10 ⁹ /L)	6.42 (3.88 – 12.02)	6.23 (4.05 – 14.70)	6.60 (3.60 – 11.96)	0.86
Lymphocyte count (x 10 ⁹ /L)	0.40 (0.26 – 0.60) (n = 13)	0.40 (0.23 – 0.83) (n = 6)	0.40 (0.21 – 0.50) (n = 7)	0.84
Influenza – Influenza A	32/34 (94.1%)	18/19 (94.7%)	14/15 (93.3%)	1.00
Influenza – Influenza B	2/34 (5.9%)	1/19 (5.3%)	1/15 (6.7%)	1.00
Influenza treatment – Oseltamivir	29/34 (85.3%)	17/19 (89.5%)	12/15 (80.0%)	0.63
Influenza – No influenza treatment	5/34 (14.7%)	2/19 (10.5%)	3/15 (20.0%)	0.63
Time between ICU admission and first positive serum GM (days)	6 (3 – 10) (n = 5)	5 (3 – ...) (n = 2)	8 (2 – ...) (n = 3)	1.00
Time between ICU admission and first positive BALF GM (days)	4 (1 – 11) (n = 27)	4 (1 – 11) (n = 16)	4 (1 – 15) (n = 11)	0.58
Time between ICU admission and first positive BALF culture (days)	4 (3 – 9) (n = 17)	5 (3 – 10) (n = 8)	4 (1 – 8) (n = 9)	0.28
Time between ICU admission and first positive TBA culture (days)	12 (7 – 19) (n = 8)	12 (8 – 13) (n = 4)	15 (6 – 26) (n = 4)	1.00
Time between ICU admission and first positive sputum culture (days)	13 (5 – 20) (n = 4)	9 (3 – ...) (n = 2)	16 (10 – ...) (n = 2)	1.00
Time between ICU admission and first positive mycological criterion for ITBA and cavitary IAPA (including PR data)	4 (1 – 9) (n = 33)	3 (1 – 6)	5 (2 – 16) (n = 14)	0.19
Time between ICU admission and first positive mycological criterion for non- cavitary IAPA	4 (1 – 10) (n = 33)	3 (1 – 6)	5 (2 – 16) (n = 14)	0.20
Early IAPA diagnosis (< 48 hours of ICU admission)	12/33 (36.4%)	8/19 (42.1%)	4/14 (28.6%)	0.49

	Total IAPA population (n = 34)	Survivors (n = 19)	Non-survivors (n = 15)	p value (survivors versus non-survivors)
Any systemic <i>Aspergillus</i> -active antifungal treatment at any time during ICU admission	29/33 (87.9%)	17/18 (94.4%)	12/15 (80.0%)	0.31
Time between influenza diagnosis and start of <i>Aspergillus</i> -active antifungal treatment (days)	4 (3 – 9) (n = 28)	3 (2 – 6) (n = 16)	6 (4 – 16) (n = 12)	0.023
Time between first positive mycological criterion and start of <i>Aspergillus</i> -active antifungal treatment (days)	1 (0 – 1) (n = 28)	1 (0 – 1) (n = 16)	1 (0 – 2) (n = 12)	0.57
Time between first physician-reported suspicion of IAPA and start of <i>Aspergillus</i> -active antifungal treatment (days)	1 (0 – 1) (n = 28)	1 (0 – 2) (n = 16)	1 (0 – 1) (n = 12)	0.66
Invasive ventilatory support at any time during ICU admission	26/29 (89.7%)	12/15 (80.0%)	14/14 (100%)	0.22
Vasopressors/inotropes at any time during ICU admission	25/29 (86.2%)	11/15 (73.3%)	14/14 (100%)	0.10
AKI at any time during ICU admission	21/33 (63.6%)	10/18 (55.6%)	11/15 (73.3%)	0.47
RRT at any time during ICU admission	15/33 (45.5%)	7/18 (38.9%)	8/15 (53.3%)	0.49
Any systemic corticosteroids during ICU admission	24/34 (70.6%)	10/19 (52.6%)	14/15 (93.3%)	0.020
Median cumulative corticosteroid dose during ICU admission, mg/kg prednisone equivalent	4.55 (1.38 – 12.04) (n = 24)	4.28 (1.71 – 17.69) (n = 10)	5.15 (1.28 – 11.46) (n = 14)	0.67
LOS ICU (days)	21 (9 – 45) (n = 33)	29 (5 – 51) (n = 18)	19 (12 – 34)	0.82
LOS Hospital (days)	27 (16 – 48) (n = 29)	39 (14 – 69) (n = 14)	25 (17 – 34)	0.20

Data are presented as median (IQR) or as proportions (percentages). Laboratory results obtained at the time of ICU admission.

a = Data not available for 2017/2018 cohort.

AKI = Acute kidney injury. APACHE = Acute physiology and chronic health evaluation. BALF =

Bronchoalveolar lavage fluid. BMI = Body mass index. CRP = C reactive protein. EORTC/MSGERC =

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Consortium. GM = Galactomannan. IAPA = Influenza-associated pulmonary aspergillosis. ICU = Intensive care

unit. IPA = Invasive pulmonary aspergillosis. ITBA = Invasive tracheobronchial aspergillosis. LOS = Length of

stay. PR = Physician reported (as reported directly in the electronic case report form). RRT = Renal replacement

therapy. TBA = Tracheobronchial aspirate. WBC = White blood cell count.

Supplementary Table 5. Cox regression and binary logistic regression analyses

Cox regression analysis for occurrence of IAPA or IPA in the total classifiable population (n = 216)			
Predictor variable	HR/aHR	95% Confidence interval	p value
Univariate analysis			
Influenza	2.04	0.97 – 4.25	0.06
Any EORTC host factor	1.05	0.54 – 2.07	0.88
Male sex	1.00	0.53 – 1.88	0.99
Invasive ventilatory support at any time during ICU stay	2.92	1.28 – 6.67	0.011
Any systemic corticosteroids during ICU admission	1.72	0.85 – 3.50	0.13
Multivariate analysis			
Influenza	1.40	0.62 – 3.14	0.42
Any EORTC host factor	1.13	0.51 – 2.53	0.76
Male sex	1.50	0.73 – 3.09	0.27
Invasive ventilatory support at any time during ICU stay	3.27	1.37 – 7.83	0.008
Any systemic corticosteroids during ICU admission	1.16	0.48 – 2.77	0.74
Cox regression analysis for occurrence of IAPA in the classifiable influenza population (n = 140)			
Predictor variable	HR/aHR	95% Confidence interval	p value
Univariate analysis			
Any EORTC host factor	1.13	0.52 – 2.46	0.76
Male sex	1.25	0.61 – 2.54	0.54
Invasive ventilatory support at any time during ICU stay	5.06	1.53 – 16.78	0.008
Any systemic corticosteroids during ICU admission	1.14	0.54 – 2.39	0.73
Multivariate analysis			
Any EORTC host factor	1.44	0.55 – 3.75	0.46
Male sex	1.93	0.83 – 4.47	0.13
Invasive ventilatory support at any time during ICU stay	7.03	2.03 – 24.27	0.002
Any systemic corticosteroids during ICU admission	0.66	0.27 – 1.60	0.35
Cox regression analysis for ICU mortality in the total classifiable population (n = 216)			
Predictor variable	HR/aHR	95% Confidence interval	p value
Univariate analysis			
Per 1 year increase in age	1.01	0.99 – 1.03	0.17
Male sex	1.72	0.98 – 3.03	0.06
IAPA/IPA	1.35	0.77 – 2.38	0.30
Any EORTC host factor	1.26	0.71 – 2.23	0.42
RRT at any time during ICU admission	2.21	1.28 – 3.83	0.004
Multivariate analysis			
Per 1 year increase in age	1.01	0.99 – 1.03	0.29
Male sex	1.97	1.02 – 3.78	0.042
IAPA/IPA	1.26	0.65 – 2.46	0.49
Any EORTC host factor	1.42	0.79 – 2.54	0.24
RRT at any time during ICU admission	1.88	0.93 – 3.81	0.08
Cox regression analysis for ICU mortality in the classifiable influenza population (n = 140)			
Predictor variable	HR/aHR	95% Confidence interval	p value
Univariate analysis			
Per 1 year increase in age	1.01	0.99 – 1.03	0.28
Male sex	1.78	0.91 – 3.48	0.09
IAPA	2.00	1.06 – 3.79	0.032
Multivariate analysis			
Per 1 year increase in age	1.01	0.99 – 1.04	0.25
Male sex	1.72	0.88 – 3.38	0.11
IAPA	1.99	1.05 – 3.76	0.035
Binary logistic regression analysis for IAPA or IPA occurrence in the total classifiable population (n = 216)			
Predictor variable	OR/aOR	95% Confidence interval	p value
Univariate analysis			
Influenza	2.12	0.98 – 4.57	0.056
Any EORTC host factor	1.10	0.52 – 2.32	0.80
Male sex	1.09	0.54 – 2.19	0.81
Invasive ventilatory support at any time during ICU stay	3.68	1.51 – 8.96	0.004
Any systemic corticosteroids during ICU admission	2.07	0.96 – 4.46	0.06
Multivariate analysis			
Influenza	1.48	0.59 – 3.67	0.40
Any EORTC host factor	1.22	0.48 – 3.08	0.67
Male sex	1.79	0.76 – 4.19	0.18
Invasive ventilatory support at any time during ICU stay	4.33	1.66 – 11.28	0.003

Predictor variable	OR/aOR	95% Confidence interval	p value
Any systemic corticosteroids during ICU admission	1.39	0.52 – 3.77	0.51
Binary logistic regression analysis for IAPA occurrence in the classifiable influenza population (n = 140)			
Predictor variable	OR/aOR	95% Confidence interval	p value
Univariate analysis			
Any EORTC host factor	1.12	0.45 – 2.79	0.81
Male sex	1.41	0.63 – 3.13	0.41
Invasive ventilatory support at any time during ICU stay	6.59	1.85 – 23.39	0.004
Any systemic corticosteroids during ICU admission	1.40	0.61 – 3.23	0.43
Multivariate analysis			
Any EORTC host factor	1.40	0.42 – 4.66	0.59
Male sex	2.36	0.84 – 6.62	0.10
Invasive ventilatory support at any time during ICU stay	9.81	2.51 – 38.40	0.001
Any systemic corticosteroids during ICU admission	0.73	0.23 – 2.29	0.59
Binary logistic regression analysis for ICU mortality in the total classifiable population (n = 216)			
Predictor variable	OR/aOR	95% Confidence interval	p value
Univariate analysis			
Per 1 year increase in age	1.01	0.99 – 1.04	0.33
Male sex	2.09	0.97 – 4.51	0.06
IAPA/IPA	3.07	1.47 – 6.43	0.003
Any EORTC host factor	1.00	0.44 – 2.26	1.00
RRT at any time during ICU admission	4.58	2.11 – 9.98	< 0.001
Multivariate analysis			
Per 1 year increase in age	1.01	0.98 – 1.04	0.46
Male sex	2.36	0.92 – 6.09	0.07
IAPA/IPA	3.03	1.22 – 7.53	0.017
Any EORTC host factor	1.22	0.50 – 2.95	0.66
RRT at any time during ICU admission	2.91	1.08 – 7.86	0.035
Binary logistic regression analysis for ICU mortality in the classifiable influenza population (n = 140)			
Predictor variable	OR/aOR	95% Confidence interval	p value
Univariate analysis			
Per 1 year increase in age	1.00	0.97 – 1.03	0.87
Male sex	2.84	1.13 – 7.16	0.027
IAPA	4.79	2.01 – 11.43	< 0.001
Multivariate analysis			
Per 1 year increase in age	1.01	0.98 – 1.04	0.76
Male sex	2.78	1.06 – 7.29	0.038
IAPA	4.78	1.95 – 11.67	< 0.001

aHR = Adjusted hazard ratio. aOR = Adjusted odds ratio. EORTC/MSGERC = European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium. HR = Hazard ratio. IAPA = Influenza-associated pulmonary aspergillosis. ICU = Intensive care unit. IPA = Invasive pulmonary aspergillosis. OR = Odds ratio. RRT = Renal replacement therapy.

References

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