

Figure S1: Imbalances between groups, before and after matching, measured by standardized mean differences (SMD)

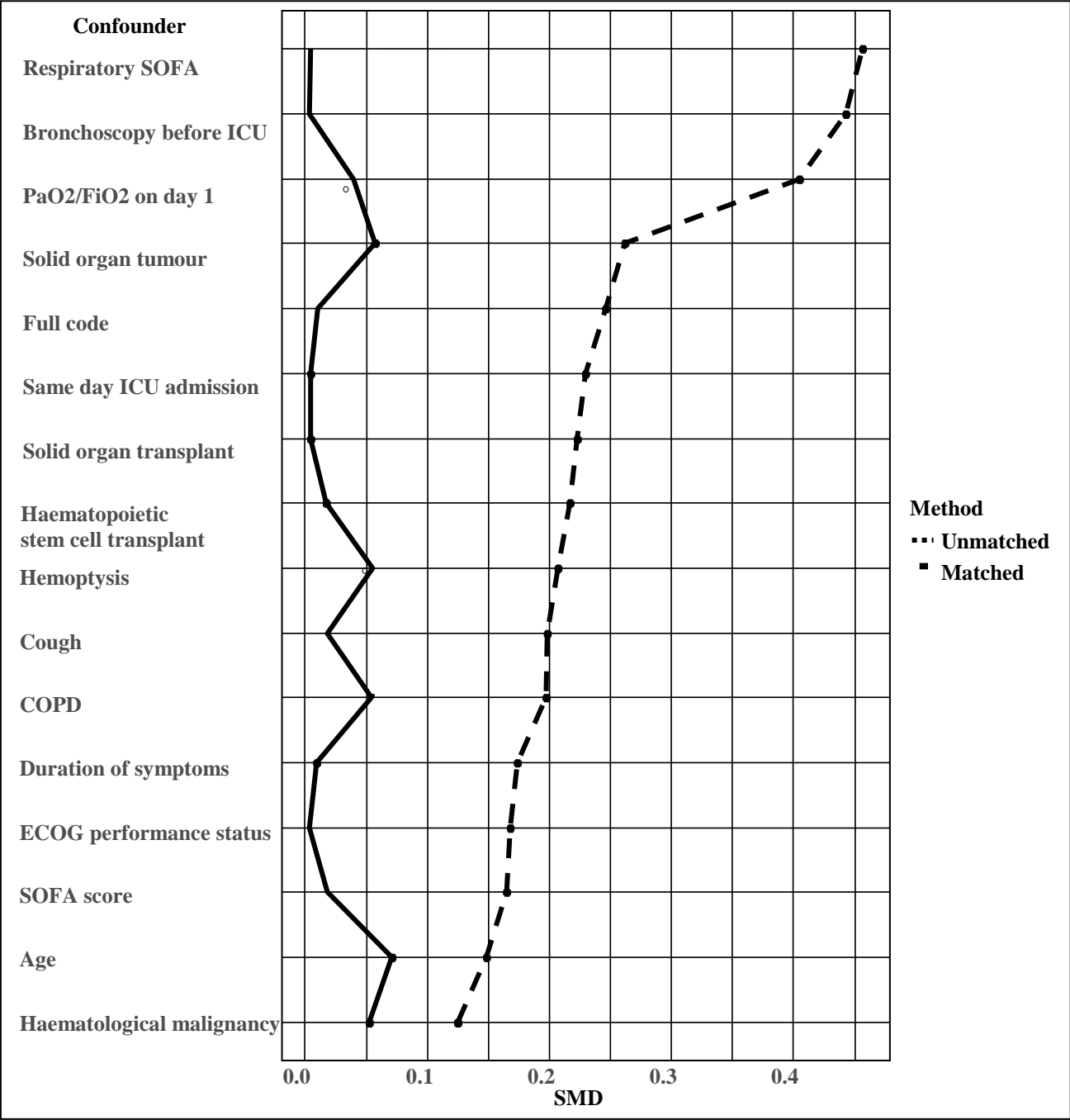


Figure S2: Distribution of the final propensity score overall and according to diagnostic group (n=494 in each group, AUC =0.498)

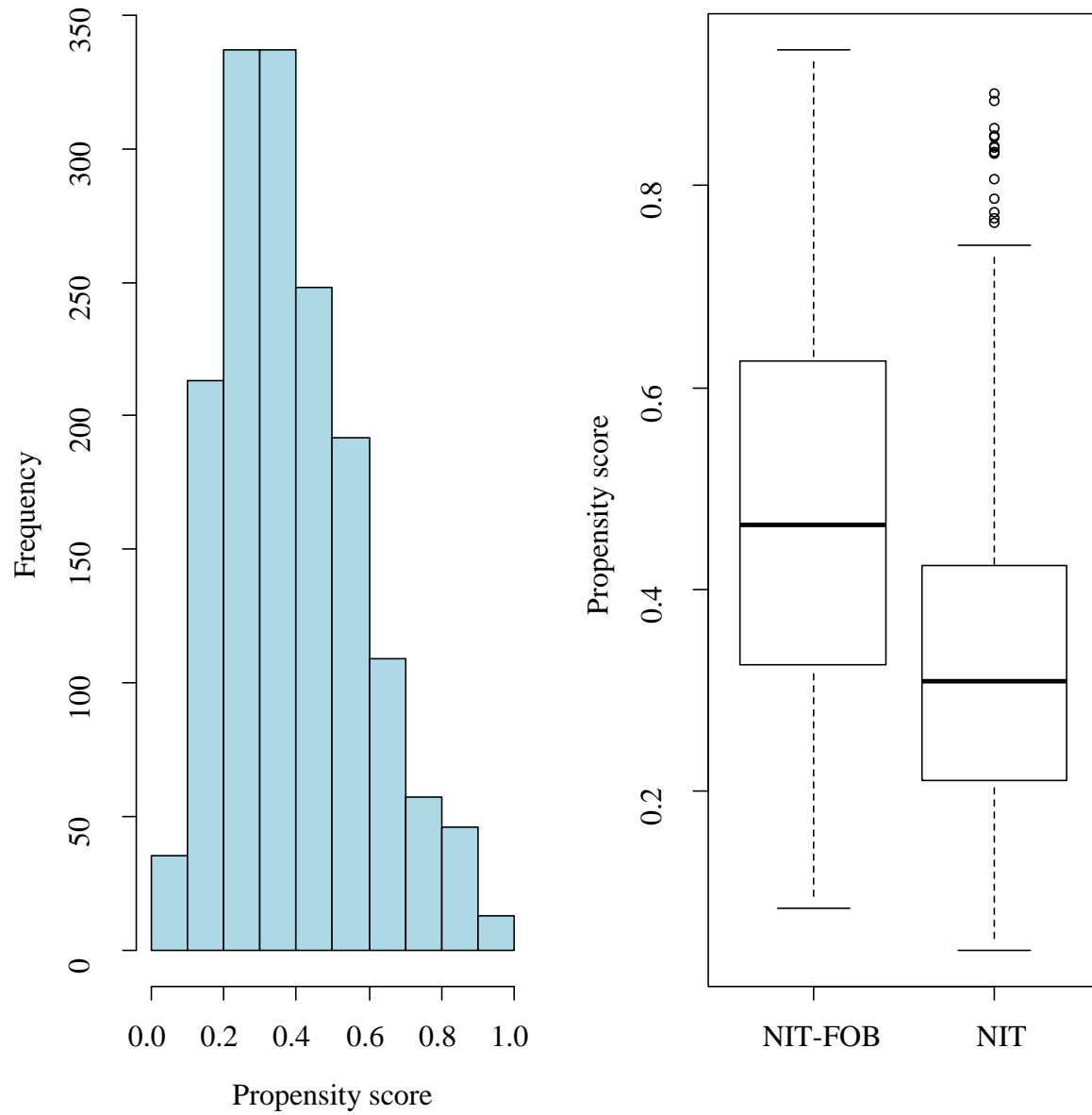


Figure S3: Hospital mortality and intubation rate by centre and expected accuracy in estimates according to centre size

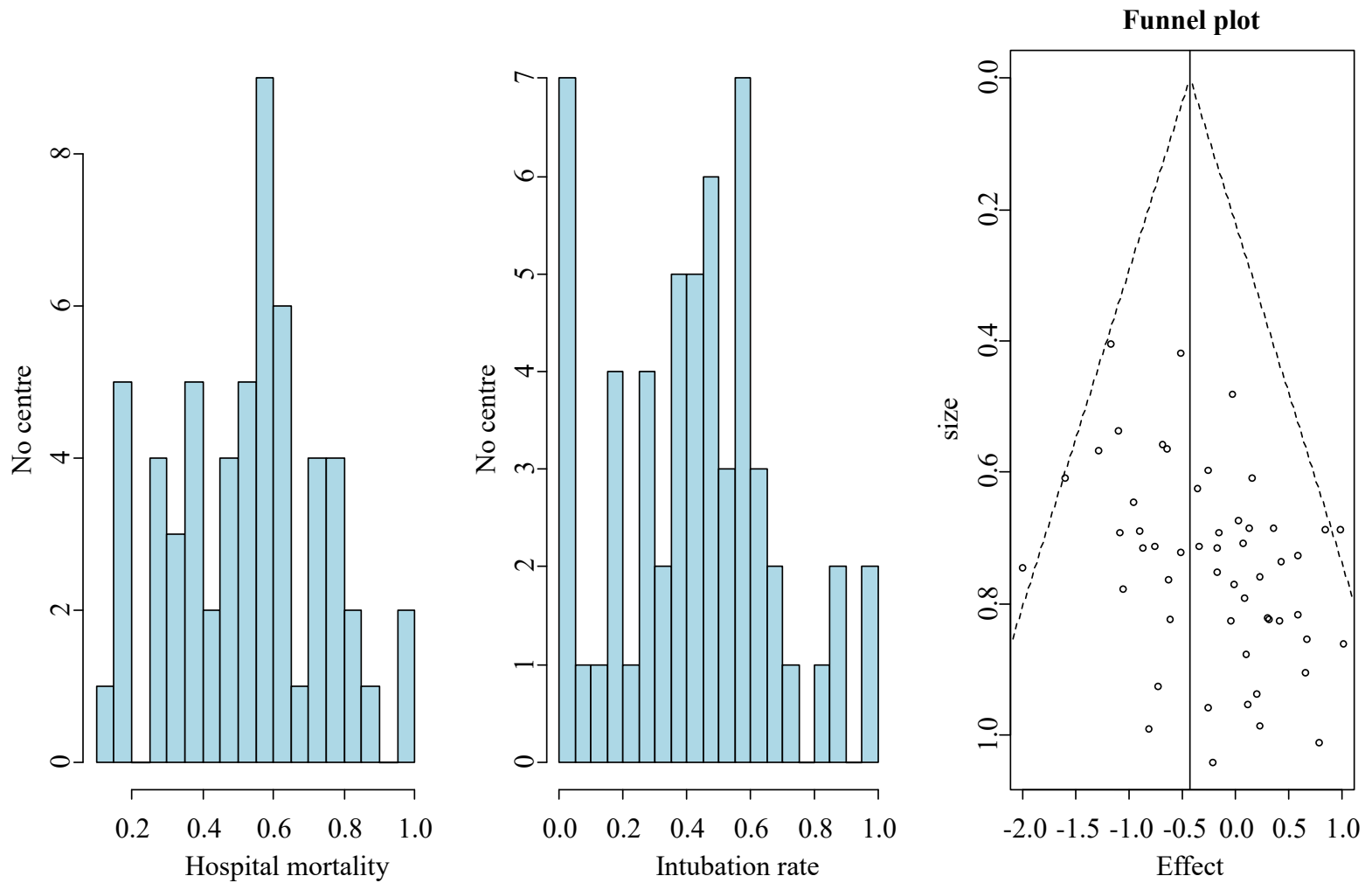


Table S1: Detailed immunosuppression according to diagnostic group (NIT: non-invasive testing only; NIT-FOB: non-invasive testing coupled with bronchoscopy; data, as available, are presented as N, percentage, or median [interquartile range])

		<b>NIT-FOB (N=618)</b>		<b>NIT (N=969)</b>		
Characteristics	Values	N	Statistics	N	Statistics	P value
Duration of disease	Days	344	166 [21;593]	595	113 [11;728]	0.34
Hematologic malignancy	Any	346	56.0%	482	49.7%	0.017
Acute myeloid leukaemia		84	13.6%	124	12.8%	
Acute lymphoblastic leukaemia		21	3.4%	30	3.1%	
Non Hodgkin lymphoma		69	11.2%	110	11.4%	
Myeloma		73	11.8%	74	7.6%	
Hodgkin lymphoma		17	2.8%	19	2.0%	
Chronic lymphocytic leukaemia		15	2.4%	36	3.7%	
Chronic myeloid leukaemia		11	1.8%	18	1.9%	
Other		56	9.1%	71	7.3%	
Disease stage status	New diagnosis	115	26.1%	213	31.8%	0.003
	1 <sup>st</sup> line therapy	73	16.6%	109	16.3%	
	> 1 <sup>st</sup> line	110	25.0%	152	22.7%	
	Remission	71	16.1%	98	14.6%	
	Uncontrolled	67	15.2%	71	10.6%	
	Palliative	4	0.9%	27	4.0%	
Haematopoietic stem cell transplantation	Autologous	44	7.1%	56	5.8%	<0.0001
	Allogeneic	82	13.3%	69	7.1%	
Systemic disease		124	20.1%	153	15.8%	0.034
Solid organ tumour		168	27.2%	382	39.4%	<0.0001
Solid organ transplant		78	14.1%	63	7.3%	<0.0001
Corticosteroid use		495	0 [0;22]	802	0 [0;15]	0.006
Neutropenia		95	16.4%	154	16.4%	1.00

Table S2: Comorbidities according to diagnostic group

		<b>NIT-FOB (N=618)</b>		<b>NIT (N 969)</b>		
<b>Characteristics</b>	<b>Values</b>	<b>N</b>	<b>Statistics</b>	<b>N</b>	<b>Statistics</b>	<b>P value</b>
Cardiac disease		122	20.9%	215	23.9%	0.19
Tobacco use		168	28.8%	287	31.0%	0.40
COPD		70	11.7%	177	18.8%	0.0003
Diabetes mellitus		113	18.9%	188	20.0%	0.66
Chronic kidney disease		91	15.1%	139	14.7%	0.88
Haemodialysis		15	2.5%	27	2.9%	0.76
Cirrhosis		28	4.7%	29	3.1%	0.13
Alcohol use		54	9.1%	93	10.0%	0.64
ECOG performance status	0	148	28.8%	161	20.9%	0.005
	1	157	30.5%	259	33.6%	
	2	123	23.9%	183	23.8%	
	3	86	16.7%	167	21.7%	
Immunization		64	13.5%	76	10.7%	0.18

ECOG: Eastern Cooperative Oncology Group

Table S3: Sequential organ failure assessment (SOFA) score according to diagnostic group

		<b>NIT-FOB N=618)</b>		<b>NIT (N=969)</b>		
<b>Characteristics</b>	<b>Values</b>	<b>N</b>	<b>Statistics</b>	<b>N</b>	<b>Statistics</b>	<b>P value</b>
SOFA score on admission		615	8 [4;10.5]	960	7 [4;10]	0.0009
Respiratory SOFA	0	47	7.9%	154	16.4%	<0.0001
	1	33	5.5%	120	12.8%	
	2	163	27.2%	298	31.7%	
	3	200	33.4%	227	24.1%	
	4	156	26.0%	142	15.1%	
Cardiovascular SOFA	0	272	44.4%	444	46.3%	0.52
	1	101	16.5%	172	17.9%	
	2	10	1.6%	22	2.3%	
	3	56	9.1%	77	8.0%	
	4	174	28.4%	245	25.5%	
Hepatic SOFA	0	435	71.2%	673	70.3%	0.93
	1	83	13.6%	139	14.5%	
	2	61	10.0%	98	10.2%	
	3	16	2.6%	28	2.9%	
	4	16	2.6%	20	2.1%	
Hematologic SOFA	0	252	41.2%	472	49.4%	0.016
	1	88	14.4%	105	11.0%	
	2	83	13.6%	125	13.1%	
	3	97	15.9%	120	12.6%	
	4	92	15.0%	134	14.0%	
Neurological SOFA	0	383	64.2%	610	65.0%	0.049
	1	105	17.6%	151	16.1%	
	2	31	5.2%	63	6.7%	
	3	24	4.0%	58	6.2%	
	4	54	9.1%	57	6.1%	
Renal SOFA	0	356	58.4%	504	52.8%	0.12
	1	116	19.0%	188	19.7%	
	2	69	11.3%	122	12.8%	
	3	35	5.7%	59	6.2%	
	4	34	5.6%	81	8.5%	

Table S4: Clinical data according to diagnostic group (NIT: non-invasive testing only; NIT-FOB: non-invasive testing coupled with bronchoscopy; data, as available, are presented as N, percentage, or median [interquartile range])

		<b>NIT-FOB (N=618)</b>		<b>NIT (N=969)</b>		
<b>Characteristics</b>	<b>Values</b>	<b>N</b>	<b>Statistics</b>	<b>N</b>	<b>Statistics</b>	<b>P value</b>
Temperature	°C	609	37.9 [36.7;38.9]	953	37.7 [36.5;38.6]	0.017
Respiratory rate	breath/minute	585	32 [25;38]	922	30 [25;36]	0.005
SpO <sub>2</sub>	%	604	91 [87;95]	947	92 [88;95]	0.016
PaO <sub>2</sub>	mm Hg	538	68 [58;83]	771	73 [60;89]	0.002
PaCO <sub>2</sub>	mm Hg	536	39 [31;50]	761	36 [29;47]	0.0009
FiO <sub>2</sub>	%	222	50 [50;83.75]	279	50 [40;70]	0.0003
O <sub>2</sub> flow	L/min	232	10 [5;15]	469	6 [3;15]	<0.0001
PaO <sub>2</sub> /FiO <sub>2</sub> on Day 1		618	140 [95;173]	969	173 [125;219]	<0.0001
≥300		42	6.8%	93	9.6%	
200-299		98	15.9%	146	15.1%	
100-199		389	62.9%	674	69.6%	
< 100		89	14.4%	56	5.8%	
Chest pain		62	11.0%	111	12.3%	0.50
Cough		277	49.4%	357	39.6%	0.0003
Purulent sputum		139	24.2%	167	18.4%	0.008
Haemoptysis		53	9.2%	37	4.1%	<0.0001
Muscle pain		37	6.5%	54	6.0%	0.77
Conjunctivitis		4	0.7%	4	0.4%	0.76
Rhinorrhoea		15	2.6%	21	2.3%	0.85
Skin rash		36	6.3%	46	5.0%	0.38
Leucocyte count	x10(9)/L	580	9 [3;16]	937	10 [3;17]	0.29
Neutrophil count	x10(9)/L	440	9 [2;23.5]	662	9 [3;20]	0.83
Platelet count	x10(9)/L	605	118 [37;223]	943	136 [41;241]	0.12
Bronchoscopy prior to ICU		98	16.6%	32	3.6%	<0.0001

Table S5: Laboratory data according to diagnostic group

		<b>NIT-FOB (N=618)</b>		<b>NIT (N=969)</b>		
<b>Characteristics</b>	<b>Values</b>	<b>N</b>	<b>Statistics</b>	<b>N</b>	<b>Statistics</b>	<b>P value</b>
<i>Blood culture</i>	Tested	582	94.3%	852	88.5%	0.0001
Blood culture	Positive	119	22.0%	223	28.7%	0.008
<i>Sputum</i>	Tested	356	57.6%	436	44.9%	<0.0001
Sputum	Positive	133	38.8%	185	45.0%	0.098
<i>Induced Sputum</i>	Tested	183	31.1%	118	12.4%	<0.0001
Induced sputum	Positive	27	14.5 %	19	15.3 %	0.97
<i>Nasopharyngeal aspirate</i>	Tested	280	46.7 %	312	32.8 %	<0.0001
Nasopharyngeal aspirate	Positive	85	32.0 %	106	36.1 %	0.35
<i>Thoracentesis</i>	Tested	71	12.0 %	104	11.0 %	0.60
Thoracentesis	Positive	14	18.4 %	27	24.3 %	0.44
<i>Biomarkers (BNP, PCT, CRP...), any</i>	Tested	479	80.5 %	691	72.9 %	0.0008
Biomarkers	Abnormal	298	83.9 %	440	84.9 %	0.76
<i>Urine antigen</i>	Tested	372	62.3 %	395	41.7 %	<0.0001
Urine antigen	Positive	17	4.7 %	38	10.1 %	0.009
<i>Serum galactomannan (or □□-D-glucan)</i>	Tested	292	50.5 %	210	22.5 %	<0.0001
Serum galactomannan (or b-D-glucan)	Positive	47	17.0 %	22	10.6 %	0.065
<i>PCR for herpes, CMV or other</i>	Tested	423	73.1 %	347	38.4 %	<0.0001
PCR for herpes, CMV or other	Positive	153	38.7 %	110	33.6 %	0.18
<i>Lung US, echocardiography, any</i>	Tested	339	66.9 %	469	53.7 %	<0.0001
Lung US, echocardiography, any	Abnormal	74	26.6 %	164	41.5 %	<0.0001
CRP on day 1	mg/L	276	118 [28;196.2]	421	77 [33;163]	0.020
CRP on day 2	mg/L	223	120 [37.5;206]	285	90 [35;181]	0.032
CRP on day 3	mg/L	198	109.5 [30;204]	255	79 [30;177.5]	0.086

BNP: brain natriuretic peptide; PCT: procalcitonin; CRP: C-reactive protein; PCR: polymerase chain reaction; CMV: cytomegalovirus; US: ultrasound



Table S6: Aetiologies according to diagnostic group; primary diagnosis refers as the main diagnosis considered by the clinician and secondary diagnosis refers to others associated with it

	<b>NIT-FOB (N=618)</b>		<b>NIT (N=969)</b>	
<b>Diagnosis</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>Primary Diagnosis</b>	<b>618</b>	<b>100</b>	<b>969</b>	<b>100</b>
Adenovirus	0	0	2	0.21
Airway issue	21	3.4	30	3.1
Aspiration	18	2.91	51	5.26
Bacterial infection	165	26.7	264	27.24
Tuberculosis	2	0.32	0	0
Candidemia	16	2.59	17	1.75
Cytomegalovirus	8	1.29	4	0.41
Chronic obstructive lung disease	3	0.49	18	1.86
Coronavirus	4	0.65	2	0.21
Drug toxicity	18	2.91	21	2.17
Enterovirus	1	0.16	0	0
Extra-pulmonary causes	30	4.85	125	12.9
Herpes simplex virus	1	0.16	0	0
Infiltrative process	62	10.03	68	7.02
Influenza	67	10.84	54	5.57
Invasive pulmonary aspergillosis	20	3.24	15	1.55
Metapneumovirus	4	0.65	2	0.21
Mucor	0	0	1	0.1
Neutrophilic recovery	0	0	1	0.1
Pulmonary edema, acute	19	3.07	80	8.26
Pneumocystis jirovecii	41	6.63	18	1.86
Pulmonary embolism	2	0.32	17	1.75
Parainfluenza virus 3	1	0.16	5	0.52
Pleural effusion	3	0.49	40	4.13
Respiratory syncytial virus	15	2.43	10	1.03
Rhinovirus	9	1.46	0	0
Trichosporon	3	0.49	0	0
Unknown	85	13.75	124	12.8
<b>Secondary diagnosis</b>	<b>499</b>	<b>80.88</b>	<b>847</b>	<b>87.41</b>
Adenovirus	2	0.32	2	0.21
Airway issue	0	0	1	0.1
Aspiration	0	0	2	0.21
Bacterial infection	15	2.43	26	2.68

Candidemia	2	0.32	2	0.21
Cytomegalovirus	2	0.32	0	0
Drug toxicity	6	0.97	7	0.72
Enterovirus	0	0	1	0.1
Fusarium	1	0.16	0	0
Infiltrative process	3	0.49	13	1.34
Influenza	19	3.08	13	1.34
Invasive fungal infection	9	1.46	10	1.03
Invasive pulmonary aspergillosis	26	4.21	3	0.31
Metapneumovirus	1	0.16	0	0
Mucor	2	0.32	0	0
Acute pulmonary oedema	3	0.49	2	0.21
Pneumocystis jirovecii	7	1.13	3	0.31
Pulmonary embolism	1	0.16	5	0.52
Parainfluenza virus 3	4	0.65	4	0.41
Pleural effusion	8	1.3	16	1.65
Reconstitution syndrome	0	0	1	0.1
Respiratory syncytial virus	5	0.81	6	0.62
Rhinovirus	2	0.32	5	0.52
Unknown	1	0.16	0	0

Table S7: Bronchoscopy procedural details and outcomes (data are presented as N, percentage)

<b>Characteristics</b>	<b>Bronchoscopy (N=618)</b>		
	<b>Present</b>	<b>Absent</b>	<b>Unknown</b>
Respiratory support during bronchoscopy	509 (82%)		109 (18%)
Standard oxygen at the time of bronchoscopy	80 (13%)	-	
High flow nasal cannula at the time of bronchoscopy	23 (4%)	-	
Non-invasive ventilation at the time of bronchoscopy	27 (4%)	-	
Intubation at the time of bronchoscopy	379 (61%)	-	
Diagnosis obtained by bronchoscopy	300 (49%)	99 (16%)	219 (35%)
Abnormal bronchial examination	210 (34%)	252 (41%)	156 (25%)
Protected bacterial distal sampling	84 (14%)	534 (86%)	-
Biopsies (bronchial or trans bronchial)	33 (5%)	507 (82%)	78 (13%)
Bronchoalveolar lavage the first line diagnostic strategy	279 (45%)	278 (45%)	61 (10%)
Bronchoscopy performed by external consultant	208 (34%)	340 (55%)	70 (11%)
Findings identified by another test	135 (22%)	377 (61%)	106 (17%)
Bronchoscopy induced change in management	236 (38%)	148 (24%)	234 (38%)
Positive test prompted new therapy	76 (12%)	-	-
Negative test allowed drug withdrawal	160 (26%)	-	-
Respiratory status worsened after bronchoscopy	70 (11%)	322 (52%)	226 (37%)

Table S8: Potential confounders of in-hospital mortality, within the first day of ICU admission, according to diagnostic group (ECOG: Eastern Cooperative Oncology Group; data are presented as N, percentage, or median [interquartile range])

		<b>NIT-FOB (N=618)</b>		<b>NIT (N=969)</b>		
<b>Characteristics</b>	<b>Values</b>	<b>N</b>	<b>Statistics</b>	<b>N</b>	<b>Statistics</b>	<b>P value</b>
Age	Years	587	62.3 [53.3;69.9]	927	64.7 [55.2;72.4]	0.0009
Duration of symptoms	Days	586	2 [0;6]	936	1 [0;3]	<0.0001
Same day ICU admission		160	26.4%	355	37.0 %	<0.0001
Hematologic malignancy		346	56.0%	482	49.7%	0.017
Solid organ tumour		168	27.2%	382	39.4%	<0.0001
Solid organ transplant		78	14.1%	63	7.3%	<0.0001
Hematopoietic stem cell transplantation	Autologous	44	7.1%	56	5.8%	<0.0001
	Allogeneic	82	13.3%	69	7.1%	
COPD		70	11.7%	177	18.8%	0.0003
ECOG performance status	0	148	28.8%	161	20.9%	0.005
	1	157	30.5%	259	33.6%	
	2	123	23.9%	183	23.8%	
	3	86	16.7%	167	21.7%	
	4	156	26.0%	142	15.1%	
Respiratory SOFA	0	47	7.9%	154	16.4%	<0.0001
	1	33	5.5%	120	12.8%	
	2	163	27.2%	298	31.7%	
	3	200	33.4%	227	24.1%	
	4	156	26.0%	142	15.1%	
SOFA score on admission		615	8 [4;10.5]	960	7 [4;10]	0.0009
Cough		277	49.4%	357	39.6%	0.0003
Haemoptysis		53	9.2%	37	4.1%	<0.0001
PaO <sub>2</sub> /FiO <sub>2</sub> on day 1		618	140 [95;173]	969	173 [125;219]	<0.0001

Table S9: Standardized mean difference (SMD) according to the diagnostic group (results are expressed as mean (SD) or n (%) as appropriate)

		<b>NIT-FOB (N=618)</b>	<b>NIT (N=969)</b>	<b>SMD</b>
<b>Characteristics</b>	<b>Values</b>	<b>Statistics</b>	<b>Statistics</b>	<b>Statistics</b>
Age	Years	60.01 (14.67)	62.24 (15.22)	0.149
Duration of symptoms	Days	5.06 (12.74)	2.82 (13.02)	0.174
Same day ICU admission,	Units	0.26 (0.44)	0.37 (0.48)	0.230
Hematologic malignancy	Units	0.56 (0.50)	0.50 (0.50)	0.125
Solid organ tumour	Units	0.27 (0.45)	0.39 (0.49)	0.262
Solid organ transplant	Units	0.14 (0.35)	0.07 (0.26)	0.222
Hematopoietic stem cell transplantation				0.217
None	Units	492 (79.6)	844 (87.1)	
Autologous	Units	44 ( 7.1)	56 ( 5.8)	
Allogeneic	Units	82 (13.3)	69 ( 7.1)	
COPD	Units	0.12 (0.32)	0.19 (0.39)	0.197
ECOG performance status	Units	1.29 (1.06)	1.46 (1.05)	0.167
Respiratory SOFA	Units	2.64 (1.15)	2.09 (1.27)	0.456
SOFA score on admission	Units	7.72 (4.13)	7.04 (4.17)	0.165
Cough	Units	0.49 (0.50)	0.40 (0.49)	0.198
Haemoptysis	Units	0.09 (0.29)	0.04 (0.20)	0.207
PaO <sub>2</sub> /FiO <sub>2</sub> on day 1	Units	152.0 (76.68)	185.8 (90.00)	0.404