

**Supplementary Table 1.** Pairwise post-hoc 2-by-2 comparisons with Holm's correction for multiplicity. Relative risk ratios were obtained from a multinomial model. Both 99% Confidence Intervals (99% CI) and P-values are adjusted to account for the three comparisons for each variable. No relative risk ratio was computed for study outcomes (ICU stay, length of stay, cost and fatal outcome).

Characteristics	Post-lung resection vs. No cancer no surgery		Cancer no surgery vs. No cancer no surgery		Post-lung resection vs. Cancer no surgery	
	Relative risk ratio (99% CI)	P	Relative risk ratio (99% CI)	P	Relative risk ratio (99% CI)	P
Gender. male	1.62 (1.38 to 1.90)	<0.0001	1.28 (1.17 to 1.41)	<0.0001	1.26 (1.09 to 1.46)	<0.0001
Age. (per decade)	0.99 (0.96 to 1.03)	0.70	1.17 (1.14 to 1.20)	<0.0001	0.85 (0.81 to 0.89)	<0.0001
Charlson Comorbidity Index (per score unit)	1.40 (1.37 to 1.44)	<0.0001	1.69 (1.65 to 1.72)	<0.0001	0.83 (0.81 to 0.85)	<0.0001
Alcohol abuse (F10*)	0.90 (0.74 to 1.10)	0.19	0.75 (0.65 to 0.87)	<0.0001	1.20 (0.95 to 1.52)	0.060
Smoking (F17*)	1.94 (1.67 to 2.25)	<0.0001	0.78 (0.70 to 0.88)	<0.0001	2.47 (2.08 to 2.94)	<0.0001
Malnutrition and/or Cachexia (E43; E44*; R64)	1.38 (1.22 to 1.57)	<0.0001	2.09 (1.91 to 2.29)	<0.0001	0.66 (0.58 to 0.76)	<0.0001
Performance status $\geq 3$ (R26.30)	0.24 (0.12 to 0.47)	<0.0001	0.88 (0.71 to 1.09)	0.14	0.27 (0.14 to 0.52)	<0.0001
Hypertension (I10)	1.21 (1.05 to 1.38)	<0.0001	0.93 (0.85 to 1.01)	0.024	1.30 (1.11 to 1.52)	<0.0001
Atherosclerosis (I25*)	1.28 (1.02 to 1.62)	0.0057	0.96 (0.82 to 1.11)	0.47	1.34 (1.03 to 1.74)	0.0035
Hyperlipidemia (E78.0-2; E78.4-5)	1.72 (1.38 to 2.16)	<0.0001	1.13 (0.94 to 1.35)	0.053	1.53 (1.22 to 1.91)	<0.0001
Atrial fibrillation (I48*)	1.30 (1.11 to 1.53)	<0.0001	1.02 (0.91 to 1.15)	0.56	1.27 (1.08 to 1.49)	0.0002
COPD (J44*; J47; J96.1*)	2.29 (1.98 to 2.66)	<0.0001	1.01 (0.91 to 1.12)	0.84	2.27 (1.91 to 2.69)	<0.0001
Sleep Apnea (G47.3)	1.21 (0.89 to 1.64)	0.13	0.77 (0.60 to 0.99)	0.009	1.57 (1.06 to 2.32)	0.003
Ascites (R18)	0.24 (0.12 to 0.49)	<0.0001	1.11 (0.89 to 1.38)	0.25	0.22 (0.10 to 0.47)	<0.0001
Pleural empyema with fistula (J860)	5.40 (4.70 to 6.21)	<0.0001	5.36 (4.93 to 5.83)	<0.0001	1.01 (0.88 to 1.15)	0.91
SAPS II (per 10 score units)	1.11 (1.08 to 1.14)	<0.0001	1.00 (0.99 to 1.02)	0.025	1.11 (1.08 to 1.14)	<0.0001
ICU	—	<0.0001	—	0.13	—	<0.0001
Length of Stay (days)	—	<0.0001	—	<0.0001	—	<0.0001
Cost. (€)	—	<0.0001	—	<0.0001	—	<0.0001
Fatal outcome	—	<0.0001	—	<0.0001	—	<0.0001

**Supplementary Table 2.** Characteristics of patients with and without fistula in the whole population and in the three subgroups.

Characteristics	Overall with fistula	Overall without fistula	p value	Post lung resection with fistula	Post lung resection without fistula	p value	Associated cancer no previous lung surgery with fistula	Associated cancer no previous lung surgery without fistula	p value	no surgery no cancer with fistula	no surgery no cancer without fistula	p value
patients. number (%)	7425	16084		1222	1077		3748	3326		2455	11681	
Male sex. number (%)	5590 (75.3%)	11268 (70.1%)	<.0001	1017 (83.2%)	788 (73.2%)	<.0001	2870 (76.6%)	2389 (71.8%)	<.0001	1703 (69.4%)	8091 (69.3%)	0.92
mean age. years (SD)	62.2 (±13.1)	62.5 (±16.6)	0.14	61.5 (±11.9)	60.8 (±13.2)	0.216	63.5 (±10.4)	66.7 (±12.2)	<.0001	60.6 (±16.6)	61.5 (±17.7)	0.0290
age classes. number (%)			0.0078			0.345			<.0001			0.0116
18-40 y	457 (6.2%)	1730 (10.8%)		67 (5.5%)	84 (7.8%)		66 (1.8%)	65 (2%)		324 (13.2%)	1581 (13.5%)	
41-60 y	2674 (36.0%)	5087 (31.6%)		447 (36.6%)	379 (35.2%)		1391 (37.1%)	917 (27.6%)		836 (34.1%)	3791 (32.5%)	
61-80 y	3757 (50.6%)	6835 (42.5%)		670 (54.8%)	574 (53.3%)		2097 (56%)	1893 (56.9%)		990 (40.3%)	4368 (37.4%)	
>80 y	537 (7.2%)	2432 (15.1%)		38 (3.1%)	40 (3.7%)		194 (5.2%)	451 (13.6%)		305 (12.4%)	1941 (16.6%)	
Charlson Comorbidity Index. mean (SD)	5.4 (±3.5)	4.0 (±3.3)	<.0001	5.7 (±3.6)	4.8 (±3.4)	<.0001	7 (±3.2)	7.7 (±3.3)	<.0001	2.9 (±2.2)	2.9 (±2.3)	0.716
Other comorbidities. number (%)												
alcohol abuse (F10*)	740 (10.0%)	1557 (9.7%)	0.493	119 (9.7%)	103 (9.6%)	0.888	354 (9.5%)	224 (6.7%)	<.0001	267 (10.9%)	1230 (10.5%)	0.613
malnutrition and/or Cachexia (E43; E44*; R64)	3235 (43.6%)	4696 (29.2%)	<.0001	492 (40.3%)	312 (29%)	<.0001	1870 (49.9%)	1302 (39.2%)	<.0001	873 (35.6%)	3082 (26.4%)	<.0001
Performance status ≥ 3 (R26.30)	181 (2.4%)	565 (3.5%)	<.0001	15 (1.2%)	5 (0.5%)	0.049	100 (2.7%)	123 (3.7%)	0.013	66 (2.7%)	437 (3.7%)	0.011
Arterial hypertension (I10)	1907 (25.7%)	4349 (27.0%)	0.029	386 (31.6%)	315 (29.3%)	0.224	889 (23.7%)	895 (26.9%)	0.0020	632 (25.7%)	3139 (26.9%)	0.25
Atherosclerosis (I25*)	520 (7%)	1077 (6.7%)	0.384	119 (9.7%)	75 (7%)	0.017	210 (5.6%)	245 (7.4%)	0.003	191 (7.8%)	757 (6.5%)	0.019
Hyperlipidemia (E78.0-2; E78.4-5)	472 (6.4%)	995 (6.2%)	0.615	121 (9.9%)	95 (8.8%)	0.376	224 (6%)	225 (6.8%)	0.175	127 (5.2%)	675 (5.8%)	0.239
Atrial fibrillation (I48*)	1274 (17.2%)	2533 (15.8%)	0.006	290 (23.7%)	159 (14.8%)	<.0001	580 (15.5%)	555 (16.7%)	0.166	404 (16.5%)	1819 (15.6%)	0.274
COPD (J44*; J47; J96.1*)	1327 (17.9%)	2294 (14.3%)	<.0001	360 (29.5%)	267 (24.8%)	0.012	538 (14.4%)	466 (14%)	0.68	429 (17.5%)	1561 (13.4%)	<.0001
Sleep Apnea (G47.3)	229 (3.1%)	477 (3.0%)	0.621	50 (4.1%)	37 (3.4%)	0.411	91 (2.4%)	82 (2.5%)	0.919	88 (3.6%)	358 (3.1%)	0.181
Ascites (R18)	154 (2.1%)	483 (3%)	<.0001	8 (0.7%)	8 (0.7%)	0.8	77 (2.1%)	144 (4.3%)	<.0001	69 (2.8%)	331 (2.8%)	0.9500
Germs. number (%)												
Escherichia coli (B96.2)	753 (10.1%)	1267 (7.9%)	<.0001	137 (11.2%)	98 (9.1%)	0.095	352 (9.4%)	375 (11.3%)	0.009	264 (10.8%)	794 (6.8%)	<.0001
Klebsiella pneumoniae (B96.1)	471 (6.3%)	520 (3.2%)	<.0001	92 (7.5%)	45 (4.2%)	7E-04	207 (5.5%)	118 (3.6%)	<.0001	172 (7%)	357 (3.1%)	<.0001

Pseudomonas (aeruginosa) (B96.5)	754 (10.2%)	790 (4.9%)	<.0001	136 (11.1%)	78 (7.2%)	0.001	381 (10.2%)	178 (5.4%)	<.0001	237 (9.7%)	534 (4.6%)	<.0001
Streptococcus (B95.0-5)	1236 (16.7%)	3013 (18.7%)	<.0001	268 (21.9%)	180 (16.7%)	0.002	520 (13.9%)	674 (20.3%)	<.0001	448 (18.3%)	2159 (18.5%)	0.785
Streptococcus A (B95.0)	48 (0.6%)	173 (1.1%)	0.0002	15 (1.2%)	7 (0.6%)	0.22	18 (0.5%)	28 (0.8%)	0.081	15 (0.6%)	138 (1.2%)	0.018
Streptococcus B (B95.1)	45 (0.6%)	118 (0.7%)	0.31	12 (1%)	7 (0.6%)	0.518	16 (0.4%)	23 (0.7%)	0.18	17 (0.7%)	88 (0.8%)	0.85
Streptococcus D (B95.2)	421 (5.7%)	539 (3.4%)	<.0001	74 (6.1%)	45 (4.2%)	0.053	199 (5.3%)	167 (5%)	0.622	148 (6%)	327 (2.8%)	<.0001
Streptococcus pneumoniae (B95.3)	97 (1.3%)	421 (2.6%)	<.0001	28 (2.3%)	29 (2.7%)	0.63	34 (0.9%)	98 (2.9%)	<.0001	35 (1.4%)	294 (2.5%)	0.001
Streptococcus. others (B95.4)	661 (8.9%)	1638 (10.2%)	0.002	156 (12.8%)	87 (8.1%)	<.0001	272 (7.3%)	351 (10.6%)	<.0001	233 (9.5%)	1200 (10.3%)	0.26
Streptococcus. unspecified (B95.5)	145 (2%)	337 (2.1%)	0.51	24 (2%)	21 (1.9%)	0.99	63 (1.7%)	63 (1.9%)	0.56	58 (2.4%)	253 (2.2%)	0.60
Staphylococcus (B95.6-8)	1148 (15.5%)	2169 (13.5%)	<.0001	263 (21.5%)	273 (25.4%)	0.03	481 (12.8%)	588 (17.7%)	<.0001	404 (16.5%)	1308 (11.2%)	<.0001
Staphylococcus Aureus (B95.6)	738 (9.9%)	1456 (9.1%)	0.03	176 (14.4%)	208 (19.3%)	0.002	277 (7.4%)	399 (12%)	<.0001	285 (11.6%)	849 (7.3%)	<.0001
Staphylococcus. others (B95.7)	482 (6.5%)	747 (4.6%)	<.0001	96 (7.9%)	74 (6.9%)	0.41	229 (6.1%)	202 (6.1%)	0.99	157 (6.4%)	471 (4%)	<.0001
Staphylococcus. unspecified (B95.8)	30 (0.4%)	63 (0.4%)	0.98	7 (0.6%)	1 (0.1%)	0.11	17 (0.5%)	22 (0.7%)	0.31	6 (0.2%)	40 (0.3%)	0.56
Other bacteria (B96.0; B96.3-4; B96.6-8*)	1391 (18.7%)	2125 (13.2%)	<.0001	289 (23.7%)	171 (15.9%)	<.0001	646 (17.2%)	498 (15%)	0.01	456 (18.6%)	1456 (12.5%)	<.0001
Length of Stay. median (IQ range) days	25 (13-47)	18 (10-30)	<.0001	33 (19-57)	22 (13-35)	<.0001	24 (11-44)	21 (11-35)	<.0001	24 (11-48)	17 (10-28)	<.0001
SAPS II. median (IQ range)	0 (0-36)	0 (0-30)	<.0001	25.5 (0-41)	15 (0-32)	<.0001	0 (0-31)	0 (0-35)	<.0001	16 (0-40)	0 (0-28)	<.0001
ICU. number (%)	1420 (19.1%)	2488 (15.5%)	<.0001	257 (21%)	140 (13%)	<.0001	474 (12.7%)	406 (12.2%)	0.576	689 (28.1%)	1942 (16.6%)	<.0001
Cost. median (IQ range) €	18 119.8 (8 222.0-38 079.7)	11 145.0 (6 262.5-20 924.0)	<.0001	31 028.5 (17 432.3-54 878.9)	19 861.0 (10 760.6-31 792.7)	<.0001	14 534.2 (6 873.1- 31 213.5)	12 545.4 (6 912.7-23 179.3)	<.0001	18 133.6 (7 839.7-39 283.9)	10 309.6 (6 011.9-18 933.4)	<.0001
Fatal outcome. number (%)	2003 (27.0%)	2007 (12.5%)	<.0001	302 (24.7%)	105 (9.8%)	<.0001	1273 (34%)	817 (24.6%)	<.0001	428 (17.4%)	1085 (9.3%)	<.0001

**Supplementary Table 3.** Multivariable analysis of factors associated with length of stay longer than 19 days (median for the whole cohort). in the whole population and in the three subgroups.

Characteristic	All patients		Post lung resection		Associated cancer no previous lung surgery		No surgery no cancer		Quantitative interaction	Qualitative interaction
	OR (99% CI)	P	OR (99% CI)	P	OR (99% CI)	P	OR (99% CI)	P	P	P
Male gender	0.89 (0.82-0.97)	0.0004	0.97 (0.72-1.32)	0.82	1.05 (0.90-1.22)	0.43	0.82 (0.74-0.91)	<0.0001	0.002	0.40
Age classes										
18-40 y	1		1		1		1			
41-60 y	0.90 (0.78-1.04)	0.063	0.56 (0.33-0.97)	0.007	0.70 (0.42-1.17)	0.075	1.01 (0.86-1.18)	0.93	0.010	0.72
61-80 y	0.69 (0.59-0.81)	<0.0001	0.42 (0.24-0.75)	0.0001	0.66 (0.39-1.10)	0.036	0.65 (0.54-0.79)	<0.0001	0.18	0.75
> 80 y	0.47 (0.39-0.57)	<0.0001	0.29 (0.12-0.69)	0.0003	0.47 (0.27-0.83)	0.0005	0.41 (0.33-0.52)	<0.0001	0.46	0.75
Charlson Comorbidity Index										
0-2	1		1		1		1			
3-4	1.37 (1.22-1.54)	<0.0001	1.42 (0.97-2.06)	0.017	0.99 (0.65-1.49)	0.94	1.56 (1.34-1.81)	<0.0001	0.029	0.72
5-6	1.91 (1.64-2.21)	<0.0001	1.76 (1.13-2.73)	0.0009	1.22 (0.79-1.87)	0.24	2.28 (1.88-2.77)	<0.0001	0.002	0.75
> 6	1.89 (1.63-2.20)	<0.0001	2.24 (1.49-3.36)	<0.0001	1.23 (0.82-1.86)	0.18	2.12 (1.66-2.71)	<0.0001	0.007	0.75
Alcohol abuse	1.51 (1.31-1.73)	<0.0001	1.57 (0.95-2.59)	0.020	1.09 (0.83-1.44)	0.41	1.71 (1.44-2.03)	<0.0001	0.002	0.75
Smoking	1.01 (0.90-1.13)	0.83	1.37 (1.00-1.87)	0.010	1.14 (0.91-1.43)	0.13	0.92 (0.79-1.06)	0.12	0.004	0.13
Malnutrition or cachexia	3.01 (2.77-3.26)	<0.0001	3.71 (2.78-4.97)	<0.0001	2.67 (2.34-3.05)	<0.0001	3.18 (2.85-3.55)	<0.0001	0.007	0.75
Performance status $\geq 3$	1.51 (1.22-1.88)	<0.0001	—	—	1.35 (0.91-2.00)	0.049	1.55 (1.19-2.01)	<0.0001	0.72	0.50
Hypertension	1.30 (1.19-1.43)	<0.0001	1.04 (0.77-1.41)	0.75	1.45 (1.23-1.70)	<0.0001	1.26 (1.12-1.42)	<0.0001	0.032	0.75
Atherosclerosis	1.32 (1.13-1.54)	<0.0001	1.12 (0.69-1.83)	0.54	1.10 (0.83-1.46)	0.40	1.46 (1.19-1.79)	<0.0001	0.080	0.75
Hyperlipidemia	1.21 (1.03-1.42)	0.003	1.03 (0.65-1.63)	0.85	1.33 (0.99-1.78)	0.014	1.17 (0.95-1.45)	0.056	0.46	0.75
Atrial fibrillation	1.81 (1.63-2.02)	<0.0001	1.83 (1.29-2.61)	<0.0001	1.96 (1.62-2.38)	<0.0001	1.73 (1.50-2.00)	<0.0001	0.41	0.75
COPD	1.29 (1.16-1.43)	<0.0001	1.55 (1.14-2.10)	0.0002	1.18 (0.97-1.44)	0.029	1.28 (1.11-1.47)	<0.0001	0.17	0.75
Sleep Apnea	1.27 (1.02-1.58)	0.006	0.82 (0.44-1.55)	0.43	1.50 (0.95-2.38)	0.023	1.29 (0.98-1.70)	0.018	0.14	0.41
Ascites	1.78 (1.39-2.27)	<0.0001	0.90 (0.20-3.98)	0.85	1.98 (1.30-3.01)	<0.0001	1.62 (1.18-2.21)	<0.0001	0.32	0.68
Fistula	1.47 (1.35-1.60)	<0.0001	1.84 (1.43-2.36)	<0.0001	1.17 (1.03-1.34)	0.002	1.71 (1.51-1.95)	<0.0001	<0.0001	0.75
Need for ICU	2.33 (2.10-2.58)	<0.0001	1.32 (0.93-1.86)	0.039	1.46 (1.19-1.80)	<0.0001	2.85 (2.51-3.24)	<0.0001	<0.0001	0.75
Study subgroup										
No surgery. no cancer	1									
Lung resection	1.72 (1.49-1.97)	<0.0001								
Associated cancer	0.97 (0.87-1.09)	0.50								

**Supplementary Table 4. Multivariable analysis of factors associated with cost higher than 12.627 € (median for the whole cohort). in the whole population and in the three subgroups.**

Characteristic	All patients		Post lung resection		Associated cancer no previous lung surgery		No surgery no cancer		Quantitative interaction	Qualitative interaction
	OR (99% CI)	P	OR (99% CI)	P	OR (99% CI)	P	OR (99% CI)	P	P	P
Male gender	0.87 (0.80-0.95)	<0.0001	0.86 (0.62-1.21)	0.26	0.97 (0.83-1.12)	0.56	0.83 (0.74-0.92)	<0.0001	0.098	0.75
Age classes										
18-40 y	1		1		1		1			
41-60 y	0.83 (0.71-0.96)	0.0007	0.57 (0.31-1.04)	0.017	0.59 (0.35-1.00)	0.009	0.92 (0.78-1.08)	0.18	0.022	0.75
61-80 y	0.61 (0.52-0.71)	<0.0001	0.36 (0.19-0.69)	<0.0001	0.52 (0.31-0.88)	0.001	0.58 (0.48-0.70)	<0.0001	0.19	0.75
> 80 y	0.31 (0.25-0.38)	<0.0001	0.30 (0.11-0.80)	0.002	0.28 (0.16-0.49)	<0.0001	0.28 (0.22-0.35)	<0.0001	0.99	0.75
Charlson Comorbidity Index										
0-2	1		1		1		1			
3-4	1.26 (1.12-1.43)	<0.0001	1.57 (1.05-2.36)	0.004	1.09 (0.72-1.66)	0.60	1.36 (1.16-1.59)	<0.0001	0.25	0.75
5-6	1.65 (1.42-1.93)	<0.0001	2.16 (1.32-3.54)	<0.0001	1.20 (0.78-1.86)	0.28	1.87 (1.53-2.29)	<0.0001	0.032	0.75
> 6	1.61 (1.38-1.89)	<0.0001	3.12 (1.96-4.97)	<0.0001	1.12 (0.74-1.69)	0.49	1.92 (1.49-2.48)	<0.0001	0.0001	0.75
Alcohol abuse	1.39 (1.21-1.61)	<0.0001	2.90 (1.34-6.25)	0.0004	1.19 (0.90-1.58)	0.11	1.43 (1.19-1.71)	<0.0001	0.016	0.75
Smoking	1.21 (1.08-1.36)	<0.0001	1.85 (1.26-2.73)	<0.0001	1.31 (1.04-1.65)	0.003	1.11 (0.95-1.28)	0.079	0.004	0.75
Malnutrition or cachexia	2.36 (2.17-2.56)	<0.0001	2.50 (1.79-3.50)	<0.0001	2.14 (1.87-2.44)	<0.0001	2.54 (2.27-2.84)	<0.0001	0.036	0.75
Performance status $\geq 3$	1.16 (0.93-1.44)	0.078	—	—	1.15 (0.78-1.69)	0.35	1.14 (0.87-1.48)	0.21	0.96	0.75
Hypertension	1.45 (1.32-1.60)	<0.0001	1.16 (0.81-1.67)	0.28	1.63 (1.38-1.93)	<0.0001	1.38 (1.22-1.56)	<0.0001	0.031	0.75
Atherosclerosis	1.41 (1.20-1.65)	<0.0001	1.21 (0.65-2.26)	0.43	1.36 (1.02-1.82)	0.006	1.41 (1.14-1.74)	<0.0001	0.83	0.75
Hyperlipidemia	1.24 (1.05-1.47)	0.0008	1.15 (0.65-2.02)	0.53	1.34 (1.00-1.81)	0.010	1.19 (0.96-1.49)	0.040	0.66	0.75
Atrial fibrillation	2.06 (1.84-2.31)	<0.0001	2.52 (1.59-4.01)	<0.0001	2.24 (1.84-2.73)	<0.0001	1.93 (1.67-2.24)	<0.0001	0.16	0.75
COPD	1.37 (1.22-1.53)	<0.0001	1.72 (1.18-2.51)	0.0002	1.16 (0.95-1.42)	0.054	1.40 (1.21-1.63)	<0.0001	0.031	0.75
Sleep Apnea	1.29 (1.02-1.62)	0.005	1.14 (0.50-2.58)	0.69	1.86 (1.15-3.01)	0.0008	1.13 (0.85-1.51)	0.26	0.068	0.75
Ascites	1.96 (1.52-2.51)	<0.0001	2.58 (0.17-40.1)	0.37	2.10 (1.37-3.19)	<0.0001	1.75 (1.27-2.40)	<0.0001	0.64	0.75
Pleural empyema with fistula	1.59 (1.46-1.74)	<0.0001	1.82 (1.36-2.43)	<0.0001	1.18 (1.03-1.35)	0.002	2.06 (1.81-2.35)	<0.0001	<0.0001	0.75
Need for ICU	5.75 (5.10-6.48)	<0.0001	2.78 (1.72-4.49)	<0.0001	3.49 (2.77-4.41)	<0.0001	7.01 (6.06-8.10)	<0.0001	<0.0001	0.75
Study subgroup										
No surgery, no cancer	1									
Lung resection	3.49 (2.99-4.07)	<0.0001								
Associated cancer	1.00 (0.89-1.12)	0.93								