German Cystic Fibrosis-Registry

Annual Report 2018

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Preface

PD Dr. med.
Lutz Nährlich

Medical Director
German CF Registry

The German Cystic Fibrosis Register is an important source of information for assessing the health status of people with cystic fibrosis in Germany. This 2018 report presents the data of 6340 people with cystic fibrosis from 90 CF sites. The proportion of adults is 58.3% and the median age is 21 years. An important CFTR genotyping in the age of mutation-specific therapies shows at least one F508del mutation in 85% of all people with cystic fibrosis. Of the people diagnosed with cystic fibrosis in 2018, 57% were diagnosed via newborn screening.

For the first time this year, transplanted patients, regardless of the type of transplantation, will be excluded from the evaluations of nutritional status, lung function, lung infections, complications and therapies. This facilitates international comparability. For the first time, the nutritional status graphically shows the age-dependent nutritional status. 83% of children (from the age of 2) and adolescents and 86% of adults have a normal nutritional status. At the age of 16-17 years 59% of the adolescents have an age-related FEV1%pred of more than 80%. A chronic Pseudomonas aeruginosa infection is detectable in 9.8% of children and adolescents and 53.1% of adults. The complications are presented for the first time as a function of age. In this way, the age dependence of complications can be better represented. The frequency of diabetes mellitus, for example, increases from 11% in 12-17 year olds to 47% in >40 year olds with cystic fibrosis. An increase in CFTR modulator therapies has been recorded. Antibiotically treated exacerbations affect 46% and CF-relevant hospitalizations 37% of all people with cystic fibrosis. The first age-dependent presentation of the care structure shows differences in the care of children and adolescents on the one hand and adults on the other. An inpatient rehabilitation measure was carried out by 8% regardless of age.

For the coming years, the volume of reports will be supplemented by observations of changes in health status, treatment and care structure over the years.

This detailed overview of the state of health of people with cystic fibrosis would not have been possible without the trust you placed in us. For this I would like to thank all ambulance teams and the people with cystic fibrosis who, with their consent, enable us to document and evaluate their data. My thanks also go to AG Register, the company Axaris (Mrs Jaumann, Mr Müller, Mr Volk) and the data management team of the Interdisciplinary Centre for Clinical Studies (IZKS) of the University of Mainz (Mrs Wosniok, Mrs Wollscheid, Mr Kronfeld, Mr Ruckes, Mr Engelmann). My special thanks go to Mr. Burkhart from the Cystic Fibrosis Institute for his tireless efforts in project management.

Please keep supporting the Registry.

Gießen, November 2019
PD Dr. med. Lutz Nährlich

Collective description

For the reporting year 2018, follow-up data records of 6340 patients will be included in the evaluations of demography, CF diagnosis, mortality and structure of care. The evaluations of CF new diagnosis and mortality also included patients without follow-up data (10 newly diagnosed and 21 deceased without follow-up data in 2018). For the first time this year the exclusion of all 348 transplanted patients from the evaluations of nutritional status, lung function, lung infections, complications and therapies, independent of the type of transplantation, is new. This results in a number of 5992 patients for the analysis of the follow-up data. For the different evaluation collectives, further definitions apply, which are described in more detail in the corresponding chapters.

A current informed consent form is available for all evaluated patients or they have died before a new informed consent could be obtained. Patients who withdrew their consent before death were excluded from the mortality analyses.

The lung function was calculated and presented using the reference values of the Global Lung Function Initiative (Quanjer et al; Eur Respir J 2012; 40: 1324).

The reference values according to the KiGGS study were used to calculate the BMI percentiles for 2-18-year-old patients (Robert Koch Institute: Reference percentiles for anthropometric measures and blood pressure from the study on the health of children and adolescents (KiGGS); Berlin: RKI-Hausdruckerei; 2013).

Missing data were not taken into account for the calculation of the percentage shares.

The follow-up data records are documented once a year in Level 1 outpatient departments as statuses for the entire calendar year or aggregated from the visit-related data records of Level 2 outpatient departments. For patients older than 6 years with a lung function measurement, the examination date selected in the year under review is the examination time with the best FEV1%pred and the corresponding body measurements. If there is no FEV1 value and for children younger than 6 years, the last available body measurements in the reporting year are used. A complication present at least once a year or a long-term therapy, microbiological evidence or a chronic infection determines the severity for the entire reporting year. If follow-up data records are available for a patient from several outpatient departments, these are also aggregated to form a data record for the report volume according to the above rules.

Contents

Map of participating CF sites within Germany in 2018

Fig. 1: Map of the participating CF sites within Germany in 2018

The map shows all 90 CF sites participating in the Register in 2018. Please report to us if your CF sites is not represented: register@muko.info. The cystic fibrosis facility in Innsbruck participates in quality assurance measures of the cystic fibrosis register. The data collected here will be used in the available Evaluation not taken into account.

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Brief overview

	2016	2017	2018
Data status	11.09.2017	18.09.2018	24.09.2019
Participating CF sites	92	91	90
Participating patients with follow-up data	5720	6106	6340
of these transplanted	281	321	348
Age in year; median	20	20	21
Proportion of adults (≥ 18 years) in %	56,8	58,1	58,3
Male patients in %	51,9	52,0	51,7
New diagnoses[1]	162	206	196
Age for new diagnoses in years; Median[1]	0,5	0,17	0,17
of these, diagnosis through new-born screening	22,8	51,9	57,1
Cases of death: number[1]	63	48	67
Cases of death: % of all patients[1]	1,1	0,8	1,1
Age of death in median years; (25.-75. P)	33 (23-41)	32 (23-39)	33 (25-42)
Transplantations	40	37	48
of these, lung transplantations[2]	36	32	45
of these, liver transplantations[2]	2	5	4

Table 1: Brief overview of cystic fibrosis patients with follow-up data, valid declaration of consent and cystic fibrosis diagnosis in the reporting year 2018 in Germany

[1] The data on new diagnoses and deaths also include cystic fibrosis patients without follow-up data.
[2] Multiple answers possible

Age structure

The calculations of the age structure include all 6340 patients with follow-up data for 2018.

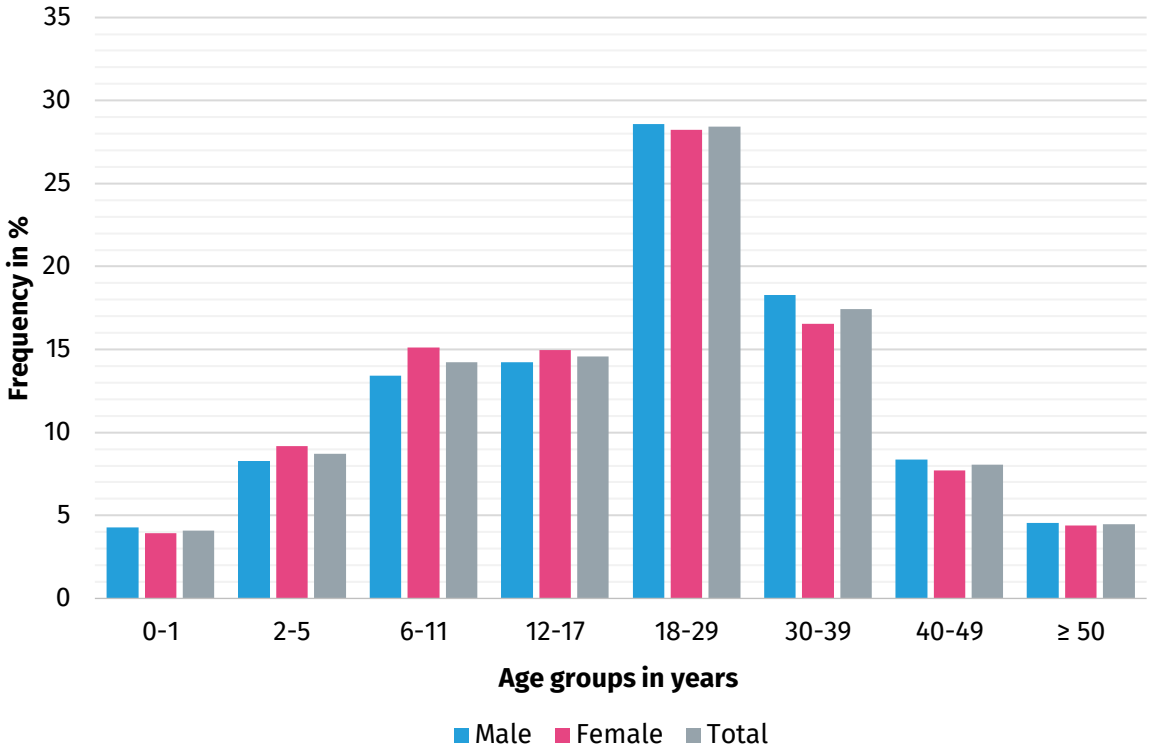

Fig. 2: Age distribution CF patients 2018

	Male	Female	Total
Number	3278	3062	6340
Mean value [years]	22,5	21,7	22,2
Median [years]	22	20	21
Minimum [years]	0	0	0
Maximum [years]	80	76	80
Perzentil 25 [years]	11	10	11
Perzentil 75 [years]	32	31	32
Number < 18 years	1319	1322	2641
Number ≥ 18 years	1959	1740	3699

Table 2: Age distribution CF patients 2018

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Age structure

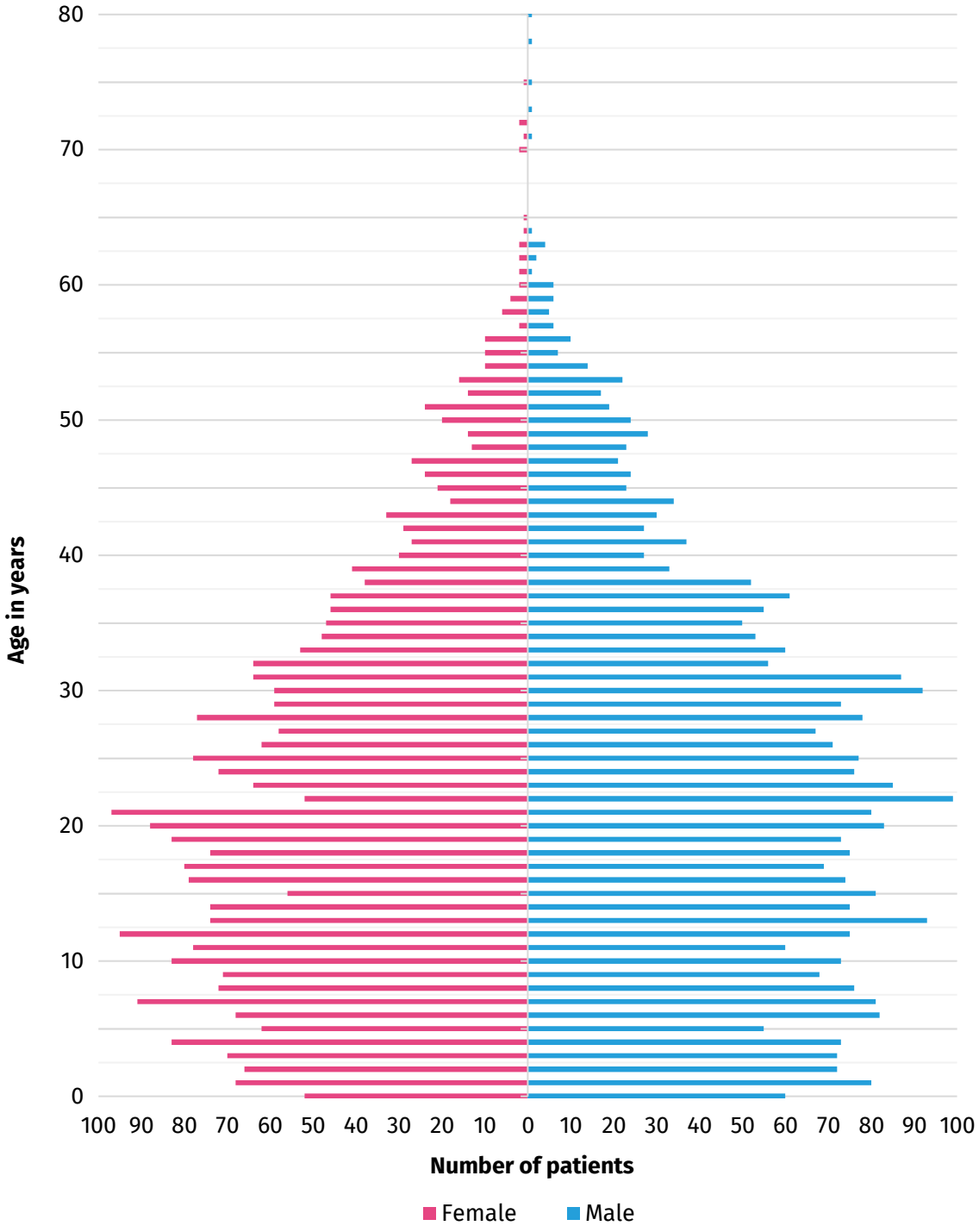

Fig. 3: Age pyramid of CF patients in 2018

CF diagnosis

4a. Diagnosis in 2018

In 2017, 196 patients were newly diagnosed, of 186 patients, follow-up data are available. The age distribution of the new diagnosed patients is shown in the following tables:

	Mean value	Median	Minimum	Maximum	25.-75.P
Age in years	4.0	0.2	0.0	62.1	0.1-2.7

Table 3: Age of new diagnosed CF patients at the time of diagnosis in 2018

Newborn screening was performed in 112 (57.1%) of newly diagnosed CF patients in 2018. 21 patients had a meconium ileus (10.7% of all patients new diagnosed in 2018).

	Mean value	Median	Min	Max	25.-75.P
Age in days	34.5	28.5	0	210	14-39

Table 4: Age of new diagnosed CF patients via newborn screening 2018

04

CF diagnosis

4a. New diagnosis in 2018

Age on diagnosis	Frequency	Percent	Accumulated percentages
0-3 month	117	60	60
4-6 month	8	4	64
7-11 month	3	2	66
1 year	8	4	70
2-5 years	31	16	86
6-11 years	9	5	91
12-17 years	8	4	95
≥ 18 years	10	5	100
Total	194	100	

Table 5: Age of diagnosed CF patients at time of diagnosis in 2018

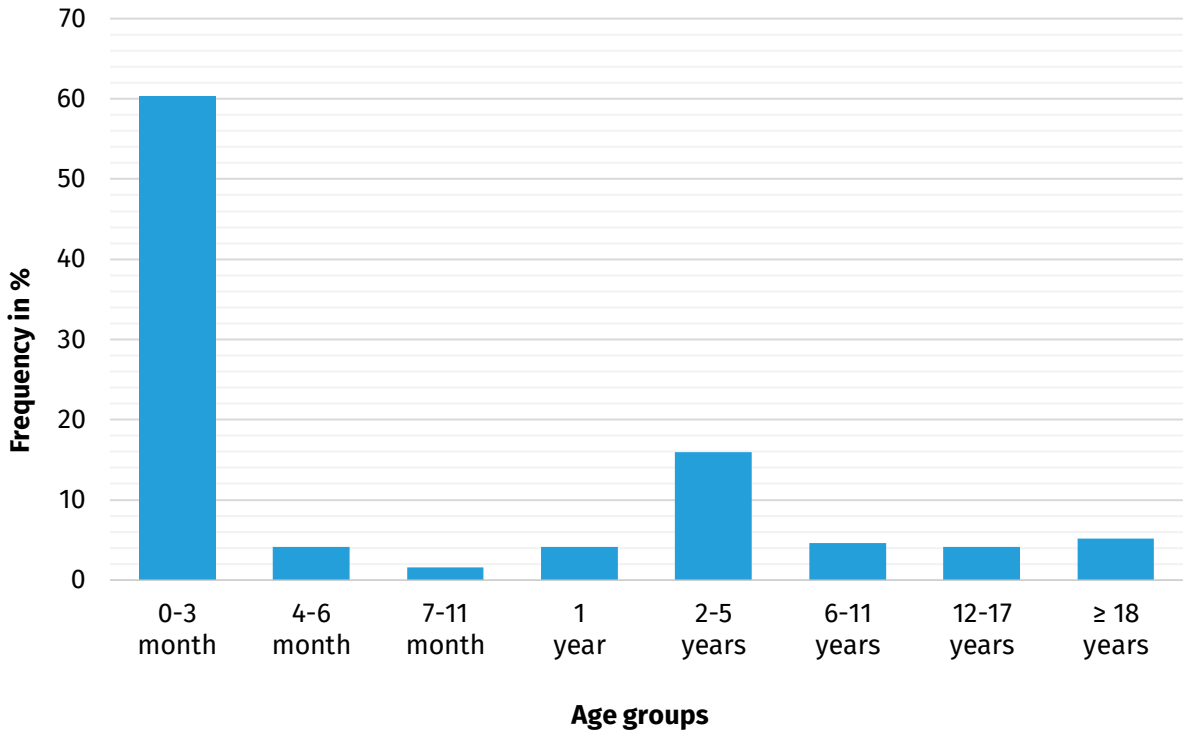

Fig. 4: Age-related frequencies in % of new diagnosed CF patients in 2018

CF diagnosis

4b. All diagnoses

The distribution of the age at diagnosis of the 6340 patients with follow-up data in 2018 is shown in the following figures and tables. A total of 244 data are missing.

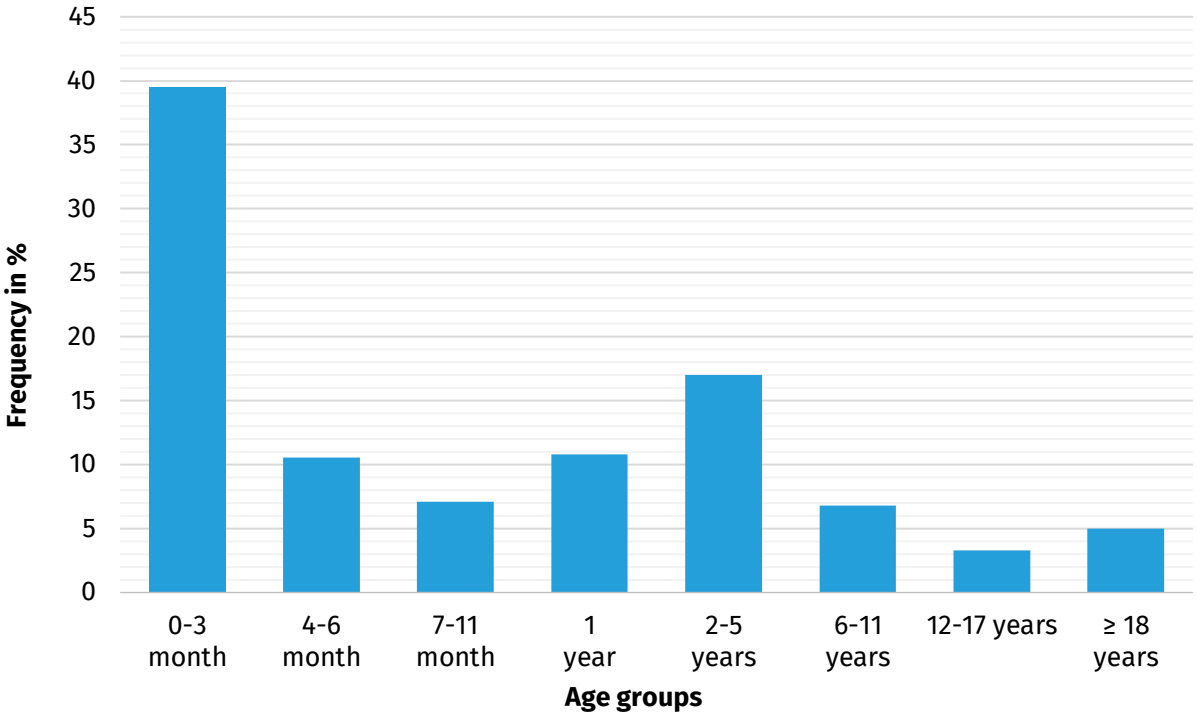

Fig.5: Age-related frequencies Age at diagnosis – all CF patients Status 2018

Age at diagnosis	Frequency	Percent	Accumulated percentages
0-3 month	2411	39.6	39.6
4-6 month	642	10.5	50.1
7-11 month	433	7.1	57.2
1 year	659	10.8	68.0
2-5 years	1035	17.0	85.0
6-11 years	413	6.8	91.7
12-17 years	200	3.3	95.0
≥ 18 years	303	5.0	100.0
unknown	244		

Table 6: Age at diagnosis - all CF patients Status 2018

04

CF diagnosis

4c. Genotyping

Genotyping is available for 6289 (99.2%) of all patients.

Mutation combinations	Frequency	Percent
F508del homozygous	2940	46.4
F508del heterozygous: Secound mutation identified	2275	35.9
F508del heterozygous: No secound mutation identified	229	3.6
No verification of F508del: Both mutations identified	717	11.3
No verification of F508del: Only one mutation identified	62	1.0
No verification of F508del: No mutationen identified	117	1.9
Total	6340	100.0

Table 7: Mutation combinations CF patients 2018

The frequencies for the individual alleles are presented below, whereby only those with an absolute frequency of at least 50 are to be individually presented:

Allel	Number	Percent
F508del (p.Phe508del / c.1521_1523delCTT)	8384	66.8
N1303K (p.Asn1303Lys / c.3909C>G)	255	2.0
G542X (p.Gly542X / c.1624G>T)	251	2.0
R553X (p.Arg553X / c.1657C>T)	239	1.9
G551D (p.Gly551Asp / c.1652G>A)	216	1.7
CFTRdele2,3 (p.Ser18ArgfsX16 / c.54-5940_273+10250del21kb)	179	1.4
R347P (p.Arg347Pro / c.1040G>C)	167	1.3
3849+10kbC->T (c.3717+12191C>T)	129	1.0
1717-1G->A (c.1585-1G>A)	104	0.8
2789+5G->A (c.2657+5G>A)	92	0.7
W1282X (p.Trp1282X / c.3846G>A)	89	0.7
2183AA->G (p.Lys684SerfsX38 / c.2051_2052delAAinsG)	83	0.7
R117H (p.Arg117His / c.350G>A)	57	0.5
3272-26A->G (c.3140-26A>G)	53	0.4
Other mutation	51	0.4
Unknown and/or not identified	1806	14.4
Total	402	3.2

Table 8: CFTR-Genotyping CF patients 2018

Nutritional status

5a. Nutritional status for children and adolescents under 18 years

All patients from 2-17 years without transplantation with follow-up data 2018 (n=2412) were considered. For 4 patients (1,7%), no nutritional status data were available. The BMI percentiles according to KiGGS were used to assess the nutritional status of children and adolescents. The age was calculated at the time of the physical examination.

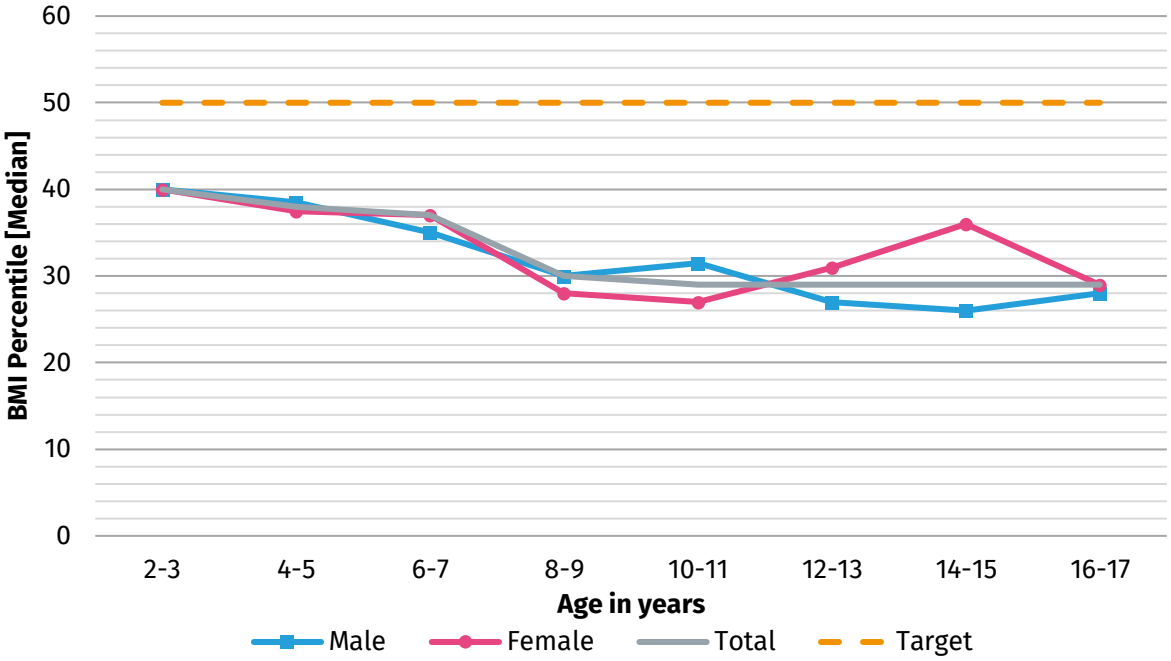

Fig. 6: Nutritional status for children and adolescents under 18 years in 2018

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
<2	298	40.0	20.0-66.0	153	40.0	22.0-66.0	145	40.0	20.0-65.0
2-3	294	38.0	16.0-61.0	144	38.5	18.5-62.5	150	37.5	15.0-58.0
4-5	322	37.0	19.0-62.0	160	35.0	17.5-61.5	162	37.0	20.0-62.0
6-7	296	30.0	17.0-51.0	146	30.0	17.0-51.0	150	28.0	17.0-53.0
8-9	301	29.0	14.0-49.0	130	31.5	14.0-53.0	171	27.0	14.0-47.0
10-11	314	29.0	12.0-54.0	166	27.0	9.0-47.0	148	31.0	14.5-56.0
12-13	286	29.0	13.0-53.0	155	26.0	11.0-48.0	131	36.0	15.0-58.0
14-15	297	29.0	10.0-52.0	138	28.0	10.0-52.0	159	29.0	10.0-53.0
16-17	2408	32.0	15.0-56.0	1192	32.0	14.0-55.0	1216	32.0	15.0-57.0
Total	298	40.0	20.0-66.0	153	40.0	22.0-66.0	145	40.0	20.0-65.0

Table 9: BMI percentile for children and adolescents under 18 years 2018

05

Nutritional status

5a. Nutritional status for children and adolescents under 18 years

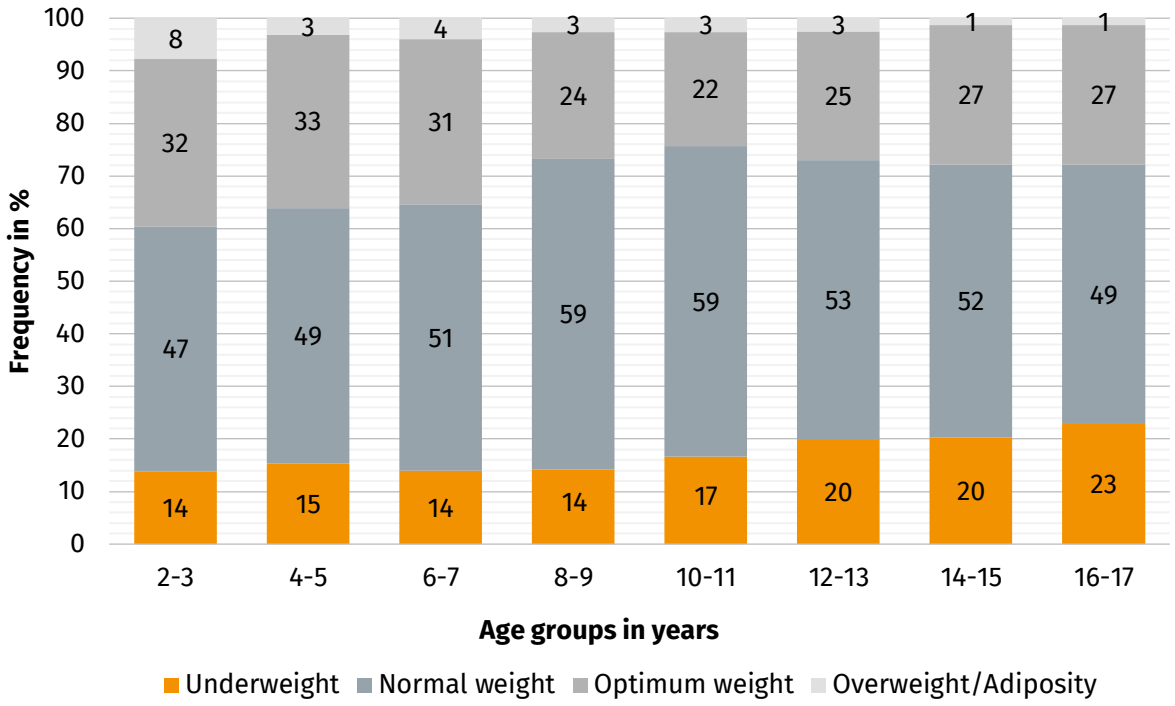

Figure 7: Nutritional status in % of children and adolescents under 18 years of age acc. BMI percentiles KIGGS 2018
Underweight: BMI percentile < 10; Normal weight: BMI percentile 10-49; Optimum weight: BMI percentile 50-89; Overweight/Adiposity: BMI percentile ≥ 90

	Male	Female	Total
Underweight	18.9	15.3	17.1
Normal weight	51.9	52.6	52.3
Optimum weight	26.1	28.8	27.5
Overweight/Obesity	3.1	3.3	3.2

Table 10: Nutritional status in % of children and adolescents under 18 years of age acc. BMI percentiles KIGGS 2018
Underweight: BMI percentile < 10; Normal weight: BMI percentile 10-49; Optimum weight: BMI percentile 50-89; Overweight/Adiposity: BMI percentile ≥ 90

Nutritional status

5b. Nutritional status for adults 18 years and older

All patients from 18 years and older without transplantation with follow-up data 2018 (n=3291) were considered. For 22 patients (0,7%), no nutritional status data were available. The age was calculated at the time of the physical examination.

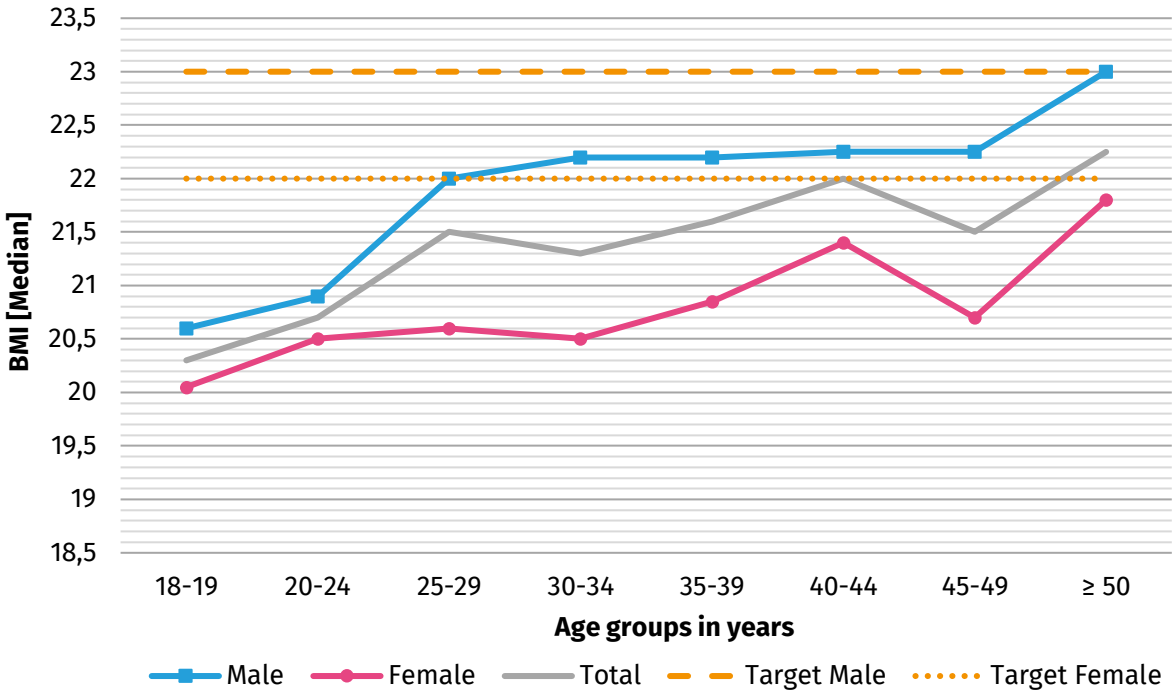

Figure 8: Nutritional status of adults 18 years and older 2018

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
18-19	287	20.3	18.8-21.9	145	20.6	19.0-22.3	142	20.1	18.7-21.5
20-24	745	20.7	18.9-22.7	390	20.9	18.9-22.9	355	20.5	18.9-22.3
25-29	654	21.5	19.7-23.5	368	22.0	20.1-24.3	286	20.6	19.1-22.4
30-34	534	21.3	19.4-23.6	279	22.2	20.3-24.5	255	20.5	18.9-22.6
35-39	385	21.6	19.7-23.9	207	22.2	20.3-25.1	178	20.9	19.1-22.8
40-44	243	22.0	20.1-23.7	138	22.3	20.9-24.1	105	21.4	19.7-23.0
45-49	193	21.5	19.9-24.0	106	22.3	20.1-24.5	87	20.7	19.6-23.2
≥ 50	228	22.3	20.4-24.6	117	23.0	21.0-25.4	111	21.8	19.8-23.9
Total	3269	21.3	19.4-23.4	1750	21.8	19.8-24.2	1519	20.7	19.0-22.6

Table 11: BMI of adults 18 years and older 2018

05

Nutritional status

5b. Nutritional status for adults from 18 years and older

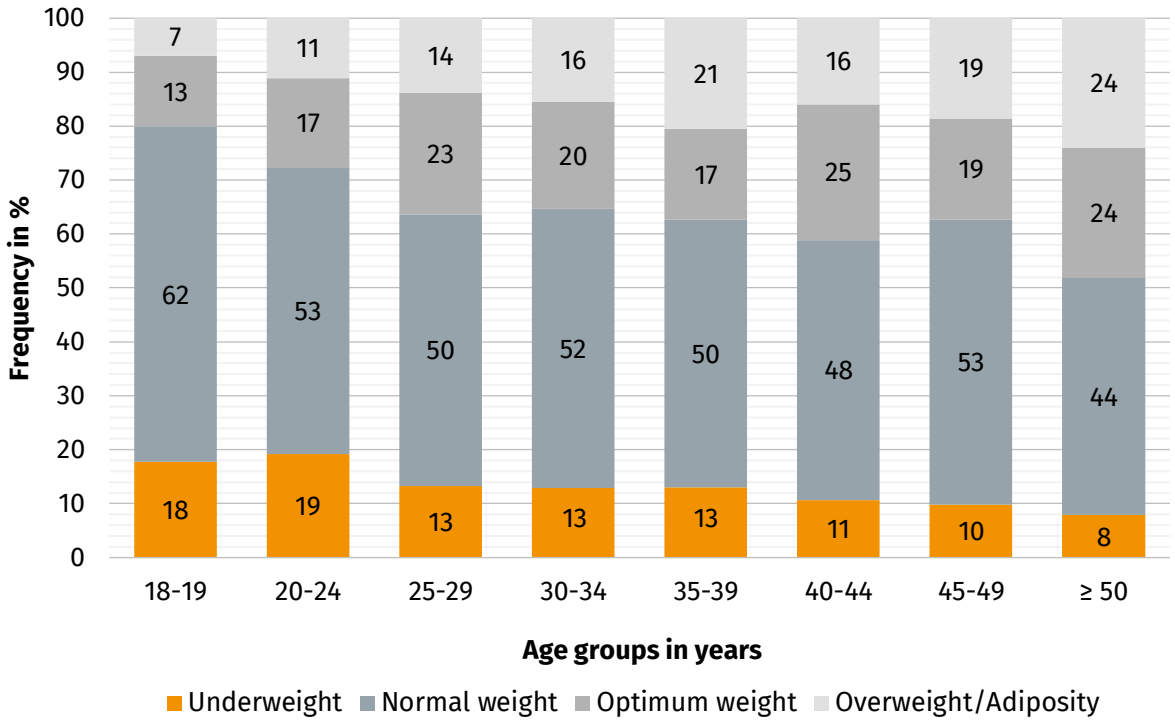

Figure 9: Nutrition status in % of adults 18 years and older 2018
Underweight: BMI < 18.5 kg/qm; Normal weight: Men: BMI 18.5 kg/qm -22.9kg/qm; Women: BMI 19.0-21.9 kg/sqm;
Optimal weight: BMI men 23.0 kg/qm-24.9 kg/qm, BMI women 22.0-24.9 kg/qm; Overweight/Adiposity: BMI ≥ 25 kg/qm

BMI	Male	Female	Total
Underweight	11.7	17.1	14.2
Normal weight	52.2	51.1	51.7
Optimum weight	17.6	21.3	19.3
Overweight/Obesity	18.6	10.6	14.9

Table 12: Nutrition status in % of adults 18 years and older 2018
Underweight: BMI < 18.5 kg/qm; Normal weight: Men: BMI 18.5 kg/qm -22.9kg/qm; Women: BMI 19.0-21.9 kg/sqm;
Optimal weight: BMI men 23.0 kg/qm-24.9 kg/qm, BMI women 22.0-24.9 kg/qm; Overweight/Adiposity: BMI ≥ 25 kg/qm

Lung function

For the evaluation of lung function all patients from 6 years without transplantation, with lung function measurement 2018 were considered. A total of 4997 data sets were available.

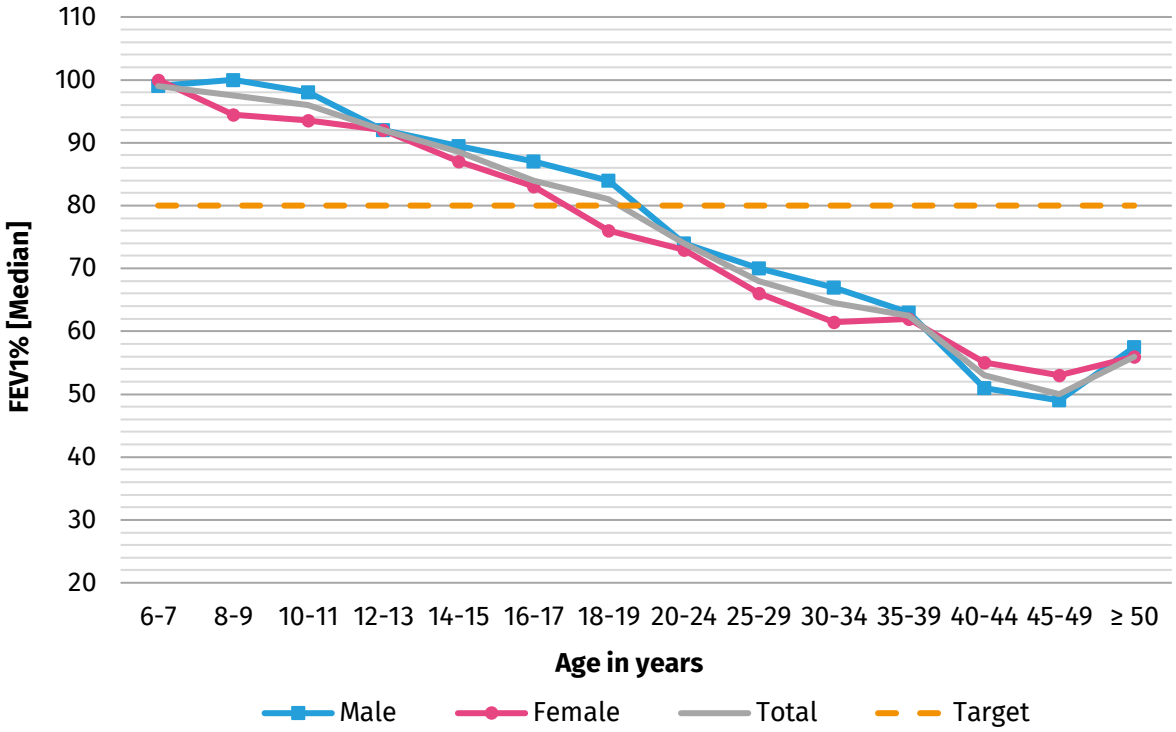

Figure 10: FEV1% value acc. Global Lung Intitiative 2018

06

Lung function

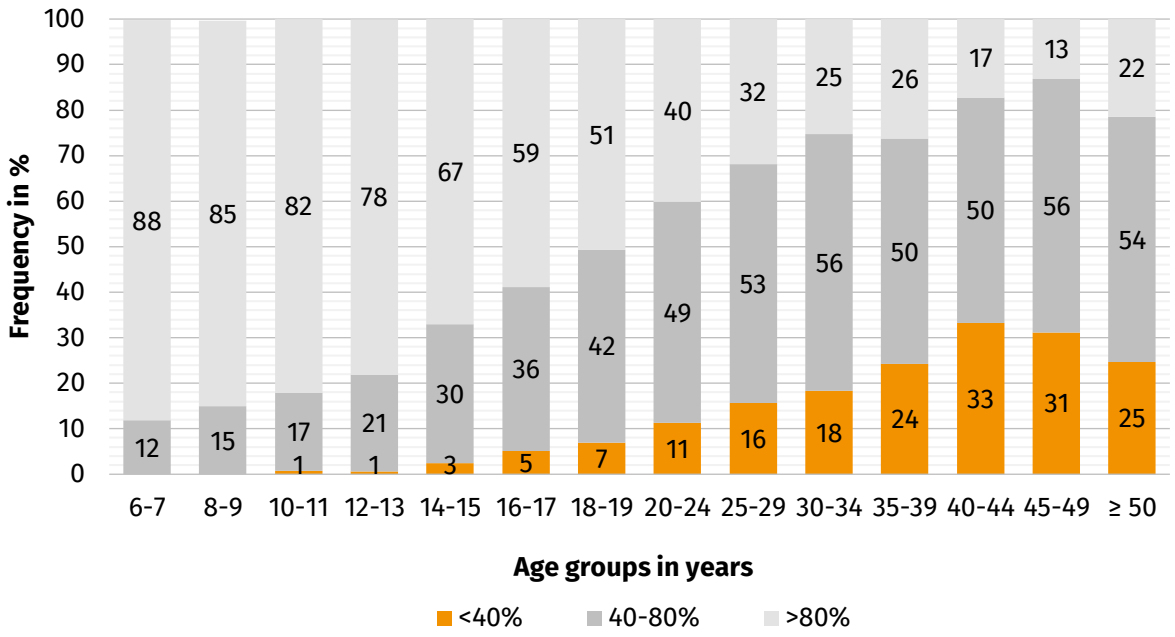

Figure 13: Age-related frequencies of severity of FEV1% (categories <40%, 40-80%, >80%) acc. Global Lung Initiative 2018

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
6-7	313	99	89-109	154	99	90-110	159	100	89-109
8-9	288	98	87-107	142	100	90-109	146	95	85-106
10-11	296	96	84-104	128	98	88-106	168	94	83-102
12-13	314	92	82-102	165	92	83-103	149	92	82-102
14-15	280	89	76-100	150	90	76-99	130	87	75-101
16-17	292	84	69-97	137	87	72-98	155	83	65-96
18-19	286	81	61-96	144	84	65-99	142	76	60-95
20-24	734	74	52-91	382	74	50-92	352	73	54-91
25-29	642	68	48-87	361	70	50-86	281	66	45-87
30-34	526	65	45-81	274	67	43-83	252	62	48-77
35-39	376	63	40-82	201	63	39-84	175	62	43-79
40-44	238	53	36-72	135	51	34-75	103	55	36-70
45-49	189	50	37-66	106	49	34-68	83	53	39-66
≥ 50	223	56	40-77	116	58	37-78	107	56	42-76
Total	4997	78	55-96	2595	79	55-96	2402	77	56-96

Table 13: FEV1% value acc. Global Lung Initiative 2018

Lung infections

7a. Detection of bacteria atleast once a year

All patients without transplantation who had at least one microbiological examination per calendar year (n=5870) were included in the evaluation of lung infections. Of 122 patients (2%), no information on the microbiological examination in the calendar year was available.

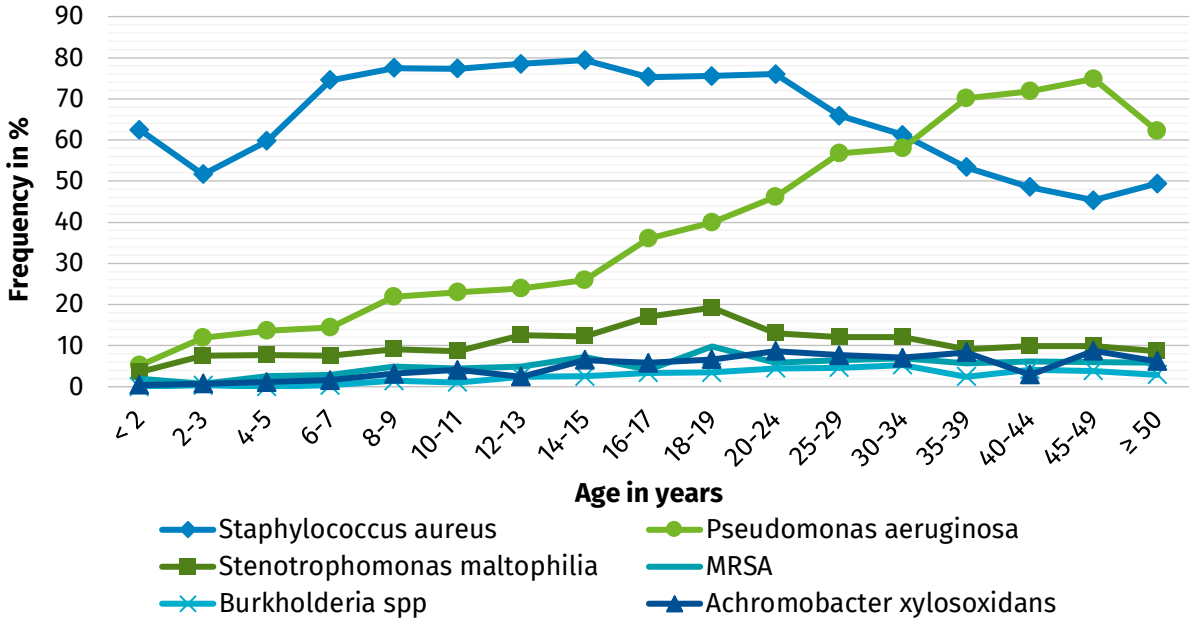

Figure 12: Age-related frequency of CF patients with bacterial detection in % with microbiological examination 2018

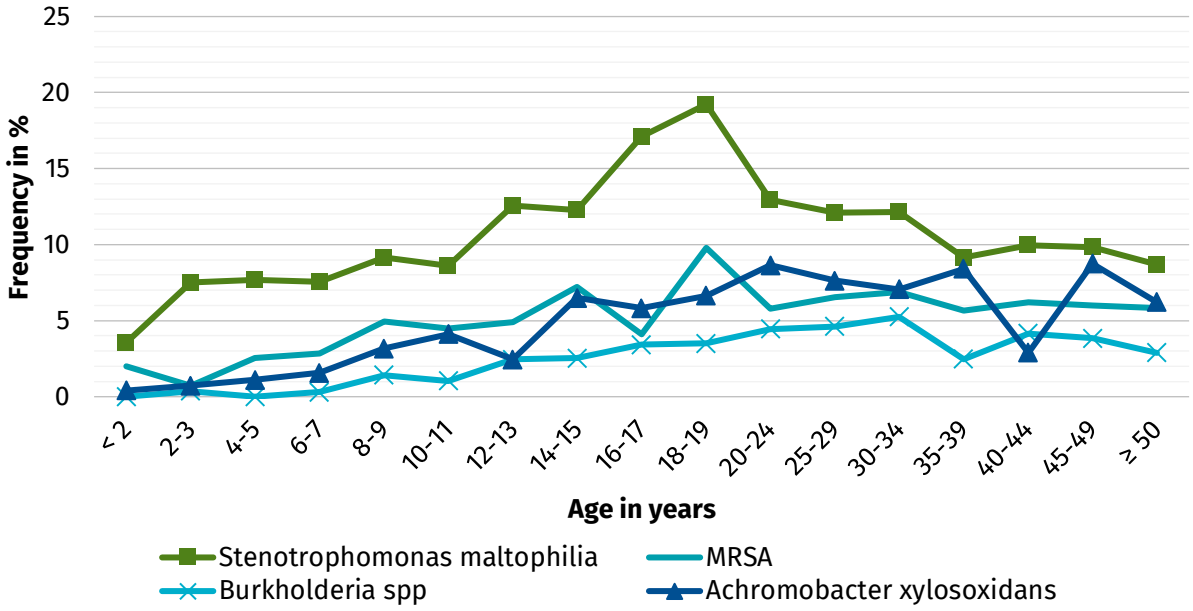

Figure 13: Age-related frequency of CF patients with bacterial detection in % with microbiological examination without Pseudomonas aeruginosa and Staphylococcus aureus 2018

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Lung infections

7a. Annual verification at least once

Age in years	Staph. Aureus	MRSA	Pseudomonas aeruginosa	Burkholderia spp	Stenotroph-omonas maltophilia	Achromobacter xylosoxidans
<2	62.5	2.0	5.1	0.0	3.6	0.4
2-3	51.6	0.7	11.8	0.4	7.5	0.7
4-5	59.7	2.6	13.6	0.0	7.7	1.1
6-7	74.5	2.8	14.5	0.3	7.6	1.6
8-9	77.5	4.9	21.8	1.4	9.2	3.2
10-11	77.3	4.5	23.0	1.0	8.6	4.1
12-13	78.5	4.9	23.9	2.5	12.6	2.5
14-15	79.4	7.2	26.0	2.5	12.3	6.5
16-17	75.3	4.1	36.0	3.4	17.1	5.8
18-19	75.5	9.8	39.9	3.5	19.2	6.6
20-24	76.0	5.8	46.2	4.5	13.0	8.6
25-29	65.9	6.5	56.7	4.6	12.1	7.6
30-34	61.2	6.9	58.0	5.3	12.1	7.1
35-39	53.3	5.7	70.1	2.5	9.1	8.4
40-44	48.6	6.2	71.8	4.2	10.0	2.9
45-49	45.4	6.0	74.9	3.8	9.8	8.7
≥ 50	49.4	5.8	62.2	2.9	8.7	6.2
Total	66.6	5.3	40.7	2.9	11.0	5.4
<18	71.1	3.8	19.8	1.3	9.7	2.9
≥ 18	63.1	6.5	57.3	4.1	12.0	7.4

Table 14: Frequency of patients with bacteria detection in % with microbiological examination 2018

Lung infections

7b. Chronic lung infection

All patients without transplantation who had at least one microbiological examination per calendar year (n=5870) were included in the evaluation of lung infections. Of 122 patients (2%), no information on the microbiological examination in the calendar year was available.

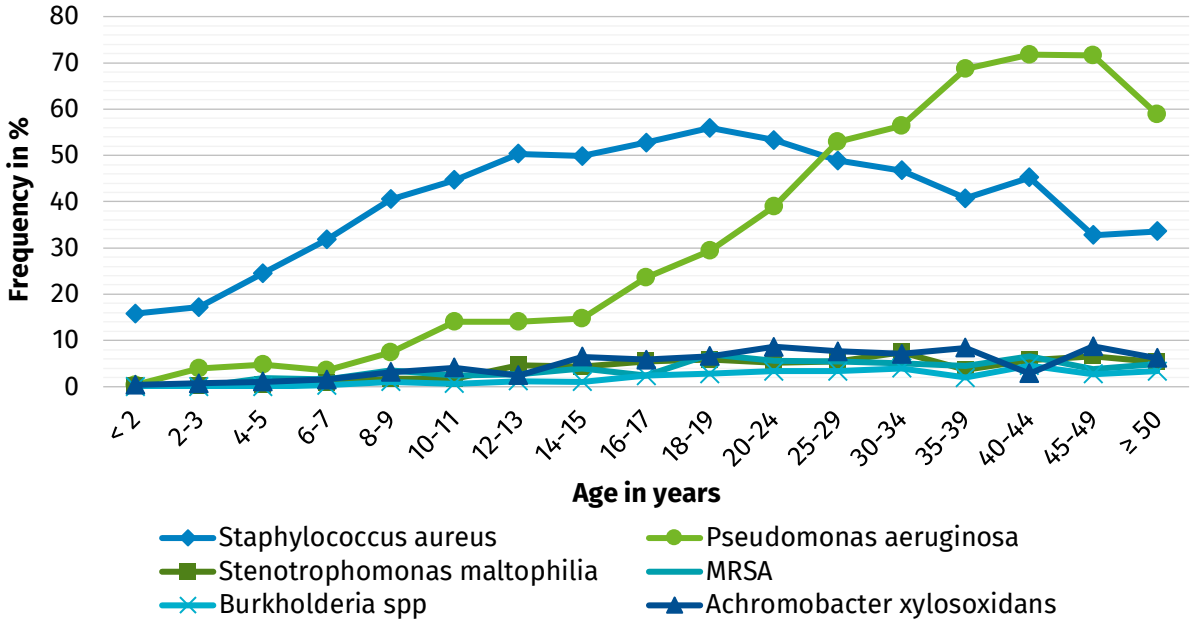

Figure 14: Age-related frequency of chronic lung infections in % of CF patients with microbiological examination 2018

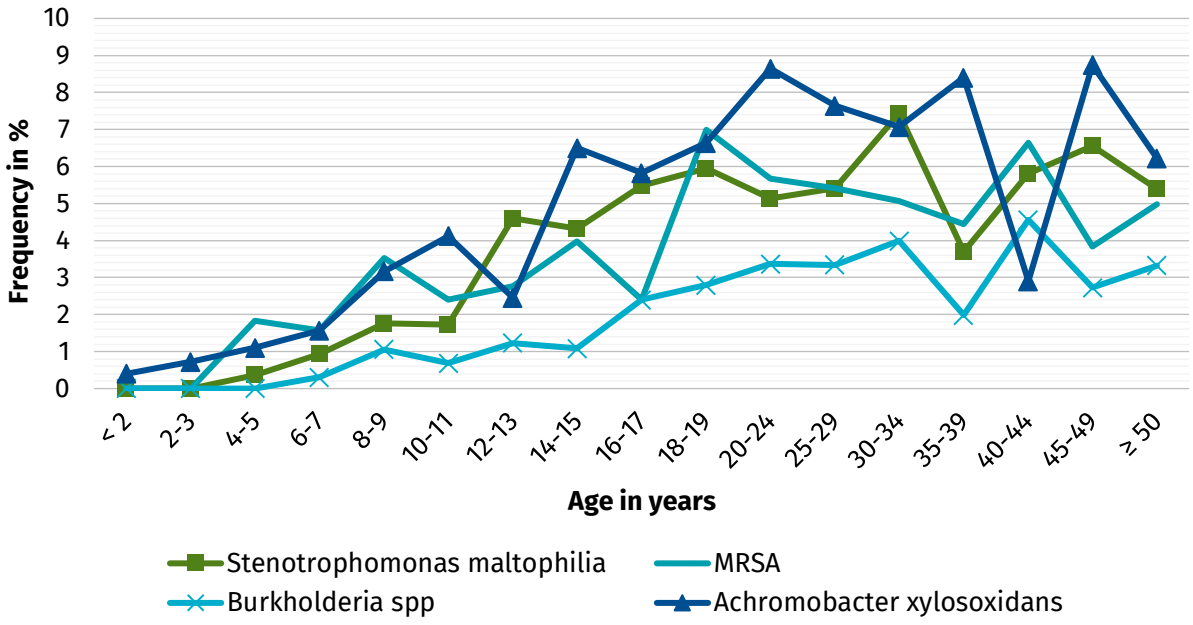

Figure 15: Age-related frequency of chronic lung infections in % of CF patients with microbiological examination without Pseudomonas aeruginosa and Staphylococcus aureus 2018

07

Lung infections

7b. Chronic lung infection

Age in years	Staph. Aureus	MRSA	Pseudomonas aeruginosa	Burkholderia spp	Stenotroph-omonas maltophilia	Achromobacter xylosoxidans
<2	15.8	0.0	0.4	0.0	0.0	0.0
2-3	17.2	0.0	3.9	0.0	0.0	0.0
4-5	24.5	1.8	4.8	0.0	0.4	0.4
6-7	31.8	1.6	3.5	0.3	0.9	0.6
8-9	40.5	3.5	7.4	1.1	1.8	1.4
10-11	44.7	2.4	14.1	0.7	1.7	2.1
12-13	50.3	2.8	14.1	1.2	4.6	1.5
14-15	49.8	4.0	14.8	1.1	4.3	3.3
16-17	52.7	2.4	23.6	2.4	5.5	3.4
18-19	55.9	7.0	29.4	2.8	5.9	4.9
20-24	53.3	5.7	39.0	3.4	5.1	6.2
25-29	48.9	5.4	52.9	3.3	5.4	5.4
30-34	46.7	5.1	56.3	4.0	7.4	6.0
35-39	40.7	4.4	68.6	2.0	3.7	7.2
40-44	45.2	6.6	71.8	4.6	5.8	3.7
45-49	32.8	3.8	71.6	2.7	6.6	5.5
≥ 50	33.6	5.0	58.9	3.3	5.4	4.6
Total	42.5	3.9	34.0	2.2	4.1	3.8
<18	36.9	2.1	9.8	0.8	2.2	1.4
≥ 18	46.8	5.4	53.1	3.3	5.6	5.7

Table 15: Frequency in % of CF patients with microbiological examination 2018

Lung infections

7c. Atypical mycobacteria

The analyses included all patients without transplantation and at least one examination for mycobacteria in 2018 (n= 2168).

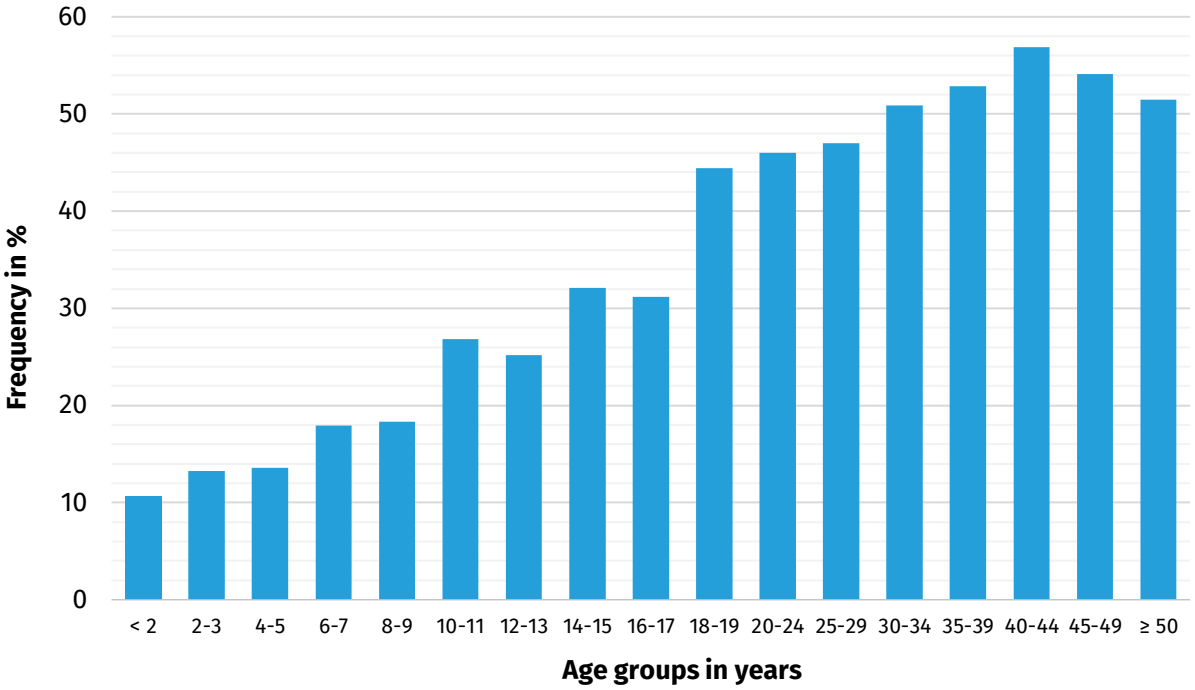

Figure 16: Age-related frequency in % of examinations for atypical mycobacteria 2018

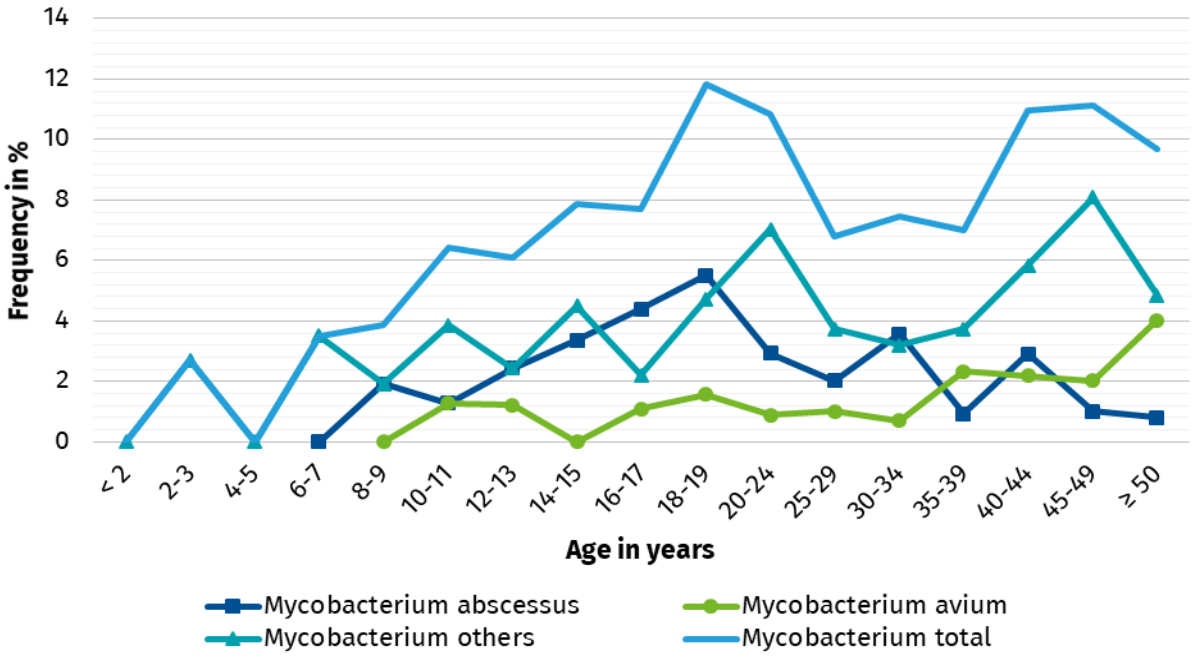

Figure 17: Age-related frequency in % of CF patients with examinations for atypical mycobacteria 2018

07

Lung infections

7c. Atypical mycobacteria (without lung transplant)

Age in years	Examination on atypical mycobacteria	Detection of		
		Mycobacterium abscessus[1]	Mycobacterium avium[1]	Mycobacterium andere[1]
<2	10.7	0.0	0.0	0.0
2-3	13.3	0.0	0.0	2.7
4-5	13.6	0.0	0.0	0.0
6-7	17.9	0.0	0.0	3.5
8-9	18.3	1.9	0.0	1.9
10-11	26.8	1.3	1.3	3.9
12-13	25.2	2.4	1.2	2.4
14-15	32.1	3.4	0.0	4.5
16-17	31.2	4.4	1.1	2.2
18-19	44.4	5.5	1.6	4.7
20-24	46.0	2.9	0.9	7.0
25-29	47.0	2.0	1.0	3.7
30-34	50.9	3.6	0.7	3.2
35-39	52.8	0.9	2.3	3.7
40-44	56.9	2.9	2.2	5.8
45-49	54.1	1.0	2.0	8.1
≥ 50	51.5	0.8	4.0	4.8
Total	36.9	2.4	1.3	4.4
<18	21.2	2.0	0.6	2.7
≥ 18	49.4	2.5	1.6	4.9

Table 16: Frequency in % of CF patients with examinations for atypical mycobacteria 2018

[1]Frequency in % of CF patients related to atypical mycobacterial examination

Complications extended

For the analysis of complications, all patients without transplantation were included who answered the question of complications. There were 2609 records of patients under 18 years and 3354 records of patients 18 years and older available. For a total of 29 patients (0.4%), questions about complications were not answered.

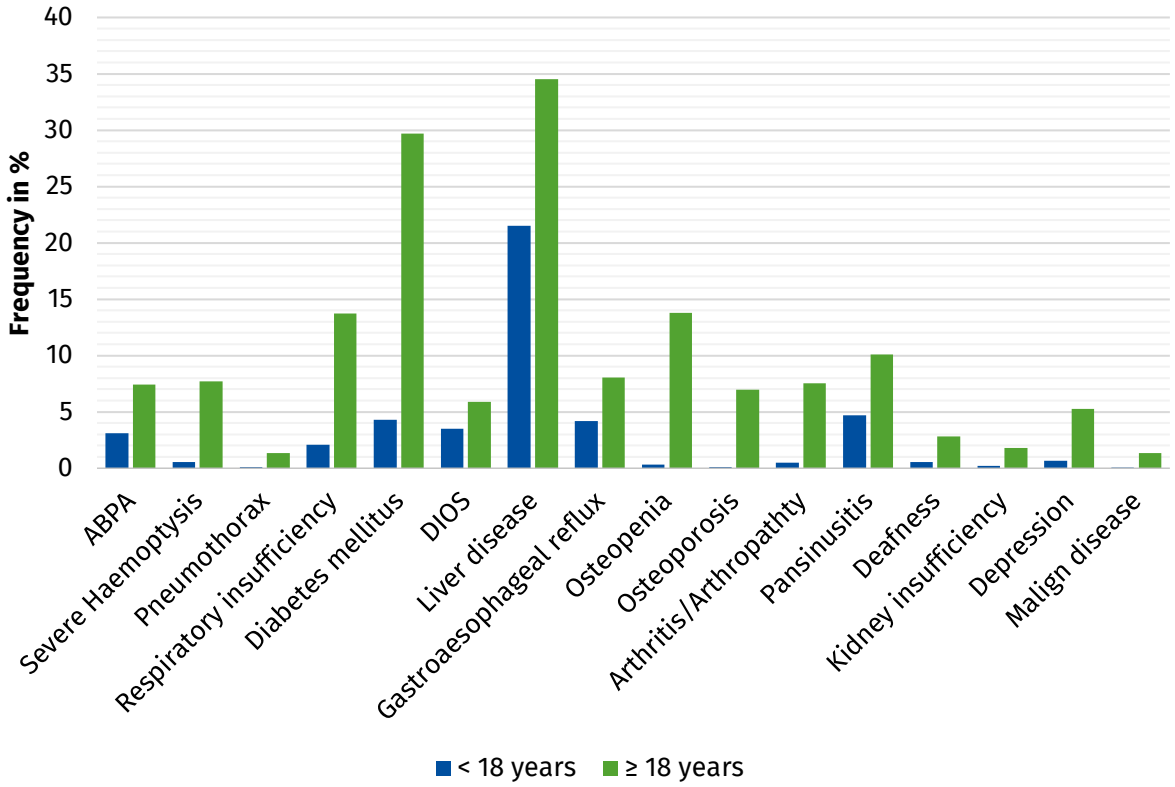

Figure 18: Frequency of various complications in % of CF patients by age groups <18 and ≥18 years without pancreatic insufficiency 2018

08

Complications extended

8a. Children and adolescents under 18 years

Complication	0-5 years	6-11 years	12-17 years	Total
ABPA	0.3	1.9	6.9	3.1
Severe Hemoptysis	0.0	0.2	1.4	0.6
Pneumothorax	0.1	0.0	0.1	0.1
of these, requiring drainage	0.0	0.0	100.0	50.0
Respiratory insufficiency	2.0	1.7	2.6	2.1
of these, partial insufficiency	62.5	86.7	69.6	72.2
of these, global insufficiency	12.5	0.0	13.0	9.3
Exocrine pancreatic insufficiency	87.8	86.4	86.2	86.8
Diabetes mellitus	0.1	1.2	11.1	4.3
of these, Typ 3	0.0	100.0	86.7	87.3
of these, not Typ 3	100.0	0.0	13.3	12.7
DIOS	3.5	3.8	3.2	3.5
Liver disease	9.6	21.4	32.4	21.5
of these, liver cirrhosis	3.9	10.9	19.9	14.6
of these, with portal hypertension	1.3	4.2	8.7	6.1
of these, without portal hypertension	2.6	3.7	6.2	4.9
Gastroesophageal reflux	2.0	4.6	5.8	4.2
Bone disease				
Osteopenia	0.0	0.0	0.9	0.3
Osteoporosis	0.0	0.0	0.3	0.1
Arthritis/Arthropathty	0.1	0.1	1.2	0.5
Pansinusitis / *Nose polyps OP in 2018*	1.0	3.7	9.0	4.7
Hearing loss	0.1	0.7	0.8	0.5
Renal insufficiency	0.0	0.0	0.6	0.2
Depression	0.0	0.1	1.8	0.7
Malign disease	0.0	0.0	0.1	0.0

Table 17: Frequencies in % of CF patients with complications under 18 years 2018

Complications extended

8b. Adults from 18 years and older

Complication	18-29 Jahre	30-39 Jahre	≥ 40 Jahre	Total
ABPA	9.0	6.4	5.2	7.5
severe Hemoptysis	6.5	9.6	8.1	7.7
Pneumothorax	1.4	1.4	1.0	1.3
of these, requiring drainage	41.7	57.1	57.1	48.9
Respiratory insufficiency	11.0	14.1	20.2	13.7
of these, partial insufficiency	72.2	75.2	69.9	72.4
of these, global insufficiency	18.2	20.4	25.7	21.1
Exocrine pancreatic insufficiency	87.1	84.9	80.7	85.2
Diabetes mellitus	21.6	32.0	46.6	29.7
of these, Typ 3	96.5	94.5	94.3	95.2
of these, not Typ 3I	3.6	5.5	5.7	4.8
DIOS	6.1	5.3	6.2	5.9
Liver disease	36.4	32.7	32.2	34.5
of these, liver cirrhosis	15.4	21.0	15.1	16.9
of these, with portal hypertension	7.8	9.5	7.6	8.2
of these, without portal hypertension	4.9	6.9	3.8	5.3
Gastroesophageal reflux	6.4	8.7	11.2	8.1
Bone disease				
Osteopenia	8.5	15.7	24.3	13.8
Osteoporosis	3.4	7.1	15.7	7.0
Arthritis/Arthropathty	4.4	9.6	12.2	7.5
Pansinusitis / Nose polyps OP in 2017	10.0	9.2	11.6	10.1
Hearing loss	1.2	3.5	5.9	2.8
Renal insufficiency	1.0	2.7	2.7	1.8
Depression	5.4	5.1	5.2	5.3
Malign disease	0.5	0.9	4.1	1.4

Table 18: Frequencies in % of CF patients with complications under 18 years 2018

08

Complications extended

8c. Antibiotically treated exacerbations

Antibiotically treated exacerbations	0	1	2	3	4	5+	unknown
0-5 years	63,0	18,1	9,2	4,2	1,8	2,6	1,1
6-11 years	60,6	19,7	10,6	4,2	2,1	2,2	0,6
12-17 years	59,0	18,1	10,2	5,3	2,8	2,7	1,9
18-29 years	49,8	20,3	11,9	6,1	4,2	5,4	2,2
30-39 years	48,8	18,6	11,8	7,2	3,6	5,7	4,3
≥ 40 years	47,9	21,9	12,2	5,3	3,0	4,9	4,7
Total	54,0	19,5	11,1	5,6	3,2	4,2	2,5
< 18 years	60,8	18,6	10,0	4,6	2,3	2,5	1,2
≥ 18 yearsre	49,1	20,2	11,9	6,3	3,8	5,4	3,4

Table 19: Frequencies of the number of antibiotically treated exacerbations per cystic fibrosis patient in the reporting year 2018 in % subdivided by age category

Therapies

For the analysis of the basic and indication therapies, all patients without transplantation were included who answered the question of long-term gastrointestinal or pulmonary therapy. The data sets of 2609 patients under the age of 18 and 3340 patients 18 years and older are included in the analyses. For 43 patients (0.7%) the question of long-term gastrointestinal or pulmonary therapy was not answered.

9a. Basic therapy

9a.i. Children and adolescents under 18 years

Basic therapy	0-5 years	6-11 years	12-17 years	Total
DNAse	13.8	55.7	68.3	47.0
Mannitol	0.0	0.5	1.3	0.6
Hypertonic saline solution	93.7	95.3	90.3	93.1
of these 0,9%	6.9	1.0	2.1	3.2
of these 1-2,9%	1.4	0.1	0.1	0.5
of these 3-5,7%	48.6	35.4	26.9	36.7
of these >=5.8%	43.0	62.9	70.6	59.3
ß2-sympathomimetics				
Short-term effect (SABA)	65.4	73.5	69.9	69.7
Long-term effect (LABA)	6.2	20.1	33.1	20.2
Anticholinergic drugs	10.5	16.7	16.9	14.8
Anti-Staphylococcus therapy	8.4	9.7	13.0	10.4
Steroids				
Nasal	6.8	24.2	23.0	18.4
Oral	0.4	2.3	5.4	2.8
Inhalative	10.4	22.5	30.7	21.6
Vitamins				
Vitamin A	82.2	81.1	81.6	81.6
Vitamin D	96.7	95.8	95.6	96.0
Vitamin E	78.1	76.1	80.4	78.2
Vitamin K	71.3	64.9	70.2	68.7

Table 20: Frequency in % of CF patients with basic therapy <18 years 2018

09

Therapies

9a. Basic therapy

9a.ii. Adults from 18 years and older

Basic therapy	18-29 years	30-39 years	≥ 40 years	Total
DNAse	63.4	55.7	48.4	58.1
Mannitol	8.7	8.7	7.0	8.4
Hypertonic saline solution	82.7	78.2	72.9	79.4
of these 0,9%	3.0	6.0	8.2	4.8
of these 1-2,9%	1.4	1.3	3.4	1.7
of these 3-5,7%	24.5	24.7	24.5	24.5
of these >=5.8%	70.5	67.7	62.4	68.2
ß2-sympathomimetics				
Short-term effect (SABA)	67.7	67.5	72.6	68.6
Long-term effect (LABA)	54.3	65.3	73.7	61.4
Anticholinergic drugs	40.1	51.5	65.0	48.4
Anti-Staphylococcus therapy	9.9	8.2	8.8	9.2
Steroids				
Nasal	22.7	19.7	18.7	21.0
Oral	8.1	10.6	14.1	10.0
Inhalative	43.7	55.4	64.0	51.2
Vitamins				
Vitamin A	75.4	67.4	57.6	69.5
Vitamin D	93.2	91.2	88.9	91.8
Vitamin E	74.5	65.1	56.1	68.0
Vitamin K	64.0	57.8	50.9	59.6

Table 21: Frequencies in % of CF patients with basic therapy >18 years 2018

Therapies

9b. Indication therapy

9b.i. Children and adolescents

Indication therapy	0-5 years	6-11 years	12-17 years	Total
CFTR Modulator	2.1	13.2	18.4	11.6
of these Ivacaftor* *in case of gating mutation*	54.6	81.6	79.2	73.8
of these Lumacaftor/Ivacaftor *In case of F508del/F508del*	0.6	19.9	31.0	18.1
Inhaled antibiotics *in case of chronic Pseudomonas infection*	72.0	90.4	91.7	89.4
of these inhalative Tobramycin	40.0	56.2	43.6	46.9
of these inhalative Colistin	48.0	61.6	61.5	60.2
of these inhalative Azetronam	0.0	12.3	16.7	13.8
of these DPI Tobramycin	0.0	1.4	14.7	9.5
of these DPI Colistin	0.0	2.7	13.5	9.1
of these Levofloxacin	0.0	0.0	2.6	1.6
others	8.0	1.4	5.1	4.3
Azithromycin *in case of chronic Pseudomonas infection*	4.0	9.6	27.6	20.1
Ursodesoxycholic acid *in case of liver disease*	80.8	90.1	88.7	88.1
Dietary measures *in case of Diabetes mellitus*	0.0	27.3	39.0	37.5
Insulin therapy *in case of Diabetes mellitus*	100.0	72.7	64.0	65.2
Orale antidiabetics *in case of Diabetes mellitus*	0.0	9.1	11.0	10.7
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	98.3	98.8	98.8	98.7
Additional formula *in case of being underweight*	37.5	60.0	62.9	55.1
Oral supplementary food	34.2	56.2	52.2	48.4
PEG	2.5	3.9	12.4	7.1
Proton pump inhibitors *in case of gastroesophageal reflux*	81.3	95.1	80.8	86.2
Polyenthylene glycol *in case of DIOS*	64.3	64.7	58.6	62.6
Calcium *in case of osteopenia/osteoporosis*	0.0	0.0	30.0	30.0
Oxygen therapy *in case of respiratory insufficiency*	18.8	26.7	43.5	31.5

Table 22: Frequency in % of patients with indication therapies < 18 years 2018

*Ivacaftor is approved in Germany from the age of 2 for gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. and from the 18th year of age, for R117H.

09

Therapies

9b. Indication therapy

9b.ii. Adults from 18 years and older

Indication therapy	18-29 years	30-39 years	≥40 years	Total
CFTR Modulator	24,6	22,6	21,6	23,4
of these Ivacaftor* *in case of gating mutation*	72,7	73,5	60,4	69,7
of these Lumacaftor/Ivacaftor *In case of F508del/F508del*	33,8	31,1	23,9	31,2
Inhaled antibiotics *in case of chronic Pseudomonas infection*	92,3	88,1	85,2	89,1
of these inhalative Tobramycin	34,3	25,8	21,3	28,1
of these inhalative Colistin	52,1	54,3	56,7	54,0
of these inhalative Azetronam	32,6	36,3	37,4	35,1
of these DPI Tobramycin	21,0	16,1	7,2	15,8
of these DPI Colistin	18,7	18,0	14,1	17,3
of these Levofloxacin	12,1	15,8	18,8	15,1
davon Andere	7,0	6,6	9,2	7,4
Azithromycin *in case of chronic Pseudomonas infection*	32,2	38,7	41,7	36,8
Ursodesoxycholic acid *in case of liver disease*	84,5	80,3	75,8	81,7
Dietary measures *in case of Diabetes mellitus*	21,0	25,0	23,3	23,0
Insulin therapy *in case of Diabetes mellitus*	67,6	76,9	75,7	73,1
Orale antidiabetics *in case of Diabetes mellitus*	9,3	9,3	8,8	9,1
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	96,7	96,0	95,6	96,3
Additional formula *in case of being underweight*	58,1	53,1	51,5	55,9
Oral supplementary food	47,9	45,3	47,0	47,1
PEG	7,8	3,9	1,5	5,9
Proton pump inhibitors *in case of gastroesophageal reflux*	79,8	77,7	81,6	79,6
Polyenthylene glycol *in case of DIOS*	51,5	34,6	40,5	44,7
Calcium *in case of osteopenia/osteoporosis*	38,0	44,1	45,8	43,0
bisphosphonates in case of osteoporosis	22,4	21,7	32,7	26,9
Oxygen therapy *in case of respiratory insufficiency*	61,5	69,3	80,3	69,4
Non-Invasive Ventilation (NIPPV) *in case of respiratory global insufficiency*	35,3	35,7	45,7	39,2

Table 23: Frequency in % of CF patients with indication therapies ≥ 18 years 2018

Mortality

Lifetime is described by median age at death, median survival and average age-specific life expectancy. Based on internationally accepted and comparable analytical methods, we would like to present these parameters in the present collective report. For the 2018 reporting year, we have decided, on account of the higher number of patients lost in follow-up, we chose to report the current median age of death for year 2018, and the median survival age and life expectancy for the period 2013–2017.

10a. Age of death 2018

The median age of death for a given year is that age at which one-half of the patients have died. In the reporting year 2018 the median age at death was 33. 67 patients (27 girls/women and 40 boys/men) died. The main causes of death were cardiopulmonary (68.7%) and malignant diseases (6.0%). Other or unknown causes were present in 25.3% of cases. The age at death is distributed as follows:

	Number	Mean value	Median	Minimum	Maximum	Perzentil 25	Perzentil 75
Age at time of death in full years	67	34,5	33	17	58	25	42

Table 24: Age of death 2018

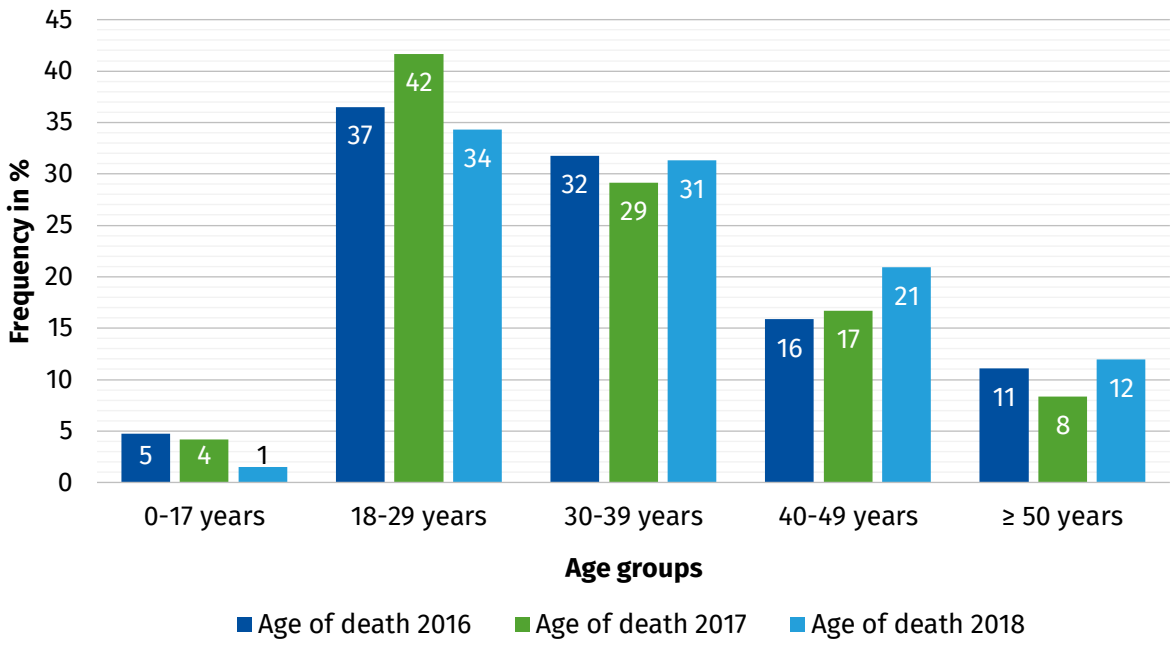

Figure 19: Frequency in % of deceased patients by age groups in 2016-2018

10

Mortality

Alter	Number	Percent
0-17 years	1	1.5
18-29 years	23	34.3
30-39 years	21	31.3
40-49 years	14	20.9
≥ 50 years	8	11.9
Total	67	100.0

Table 25: Frequency of deceased patients by age groups 2018

10b. Median survival age

The median survival age is the estimated age beyond which merely 50% of the patients will still be alive. To compensate for variations in the number of deaths per year, a COX PH regression analysis according to Sykes (Journal of Clinical Epidemiology 2016; 70: 206) is performed over a 5-year period. In the 5-year window between 2013 and 2017, 7574 people with cystic fibrosis (including transplanted patients) and 418 deaths were recorded. 48 patients (0.6%) were lost to follow-up. The median survival age amounted to 49.0 years (confidence interval: 47.1 to 52.4).

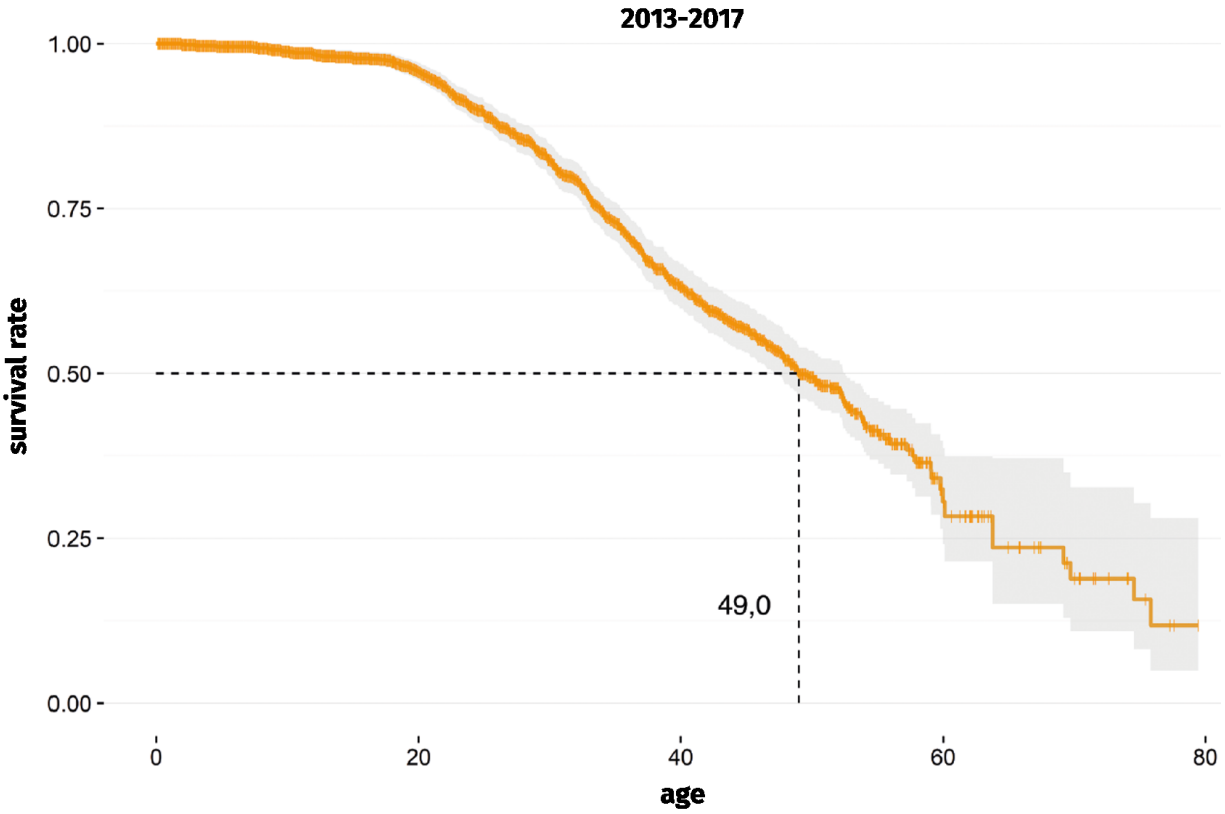

Figure 20: Median survival age for CF patients 2013-2017

Mortality

10c. Life expectancy

Life expectancy is a statistical measure of the average time a person is still expected to live (i.e. remaining time from a certain age to death). It is calculated for a given period based on current and age-specific death rates. Currently, the life expectancy of a healthy male neonate in Germany is 78 years, and that of a female neonate 83 years (www.statista.de). Life expectancy varies depending on age and does not equal the median survival age.

All parameters refer to the very heterogeneous population of cystic fibrosis patients in Germany. Hence, they allow only limited conclusions regarding the individual patients. According to the literature, the key influencing factors include the patient's age, the gene mutation present and the exocrine pancreatic function. All calculations based on the current death rate, which has fortunately been steadily decreasing over the past years.

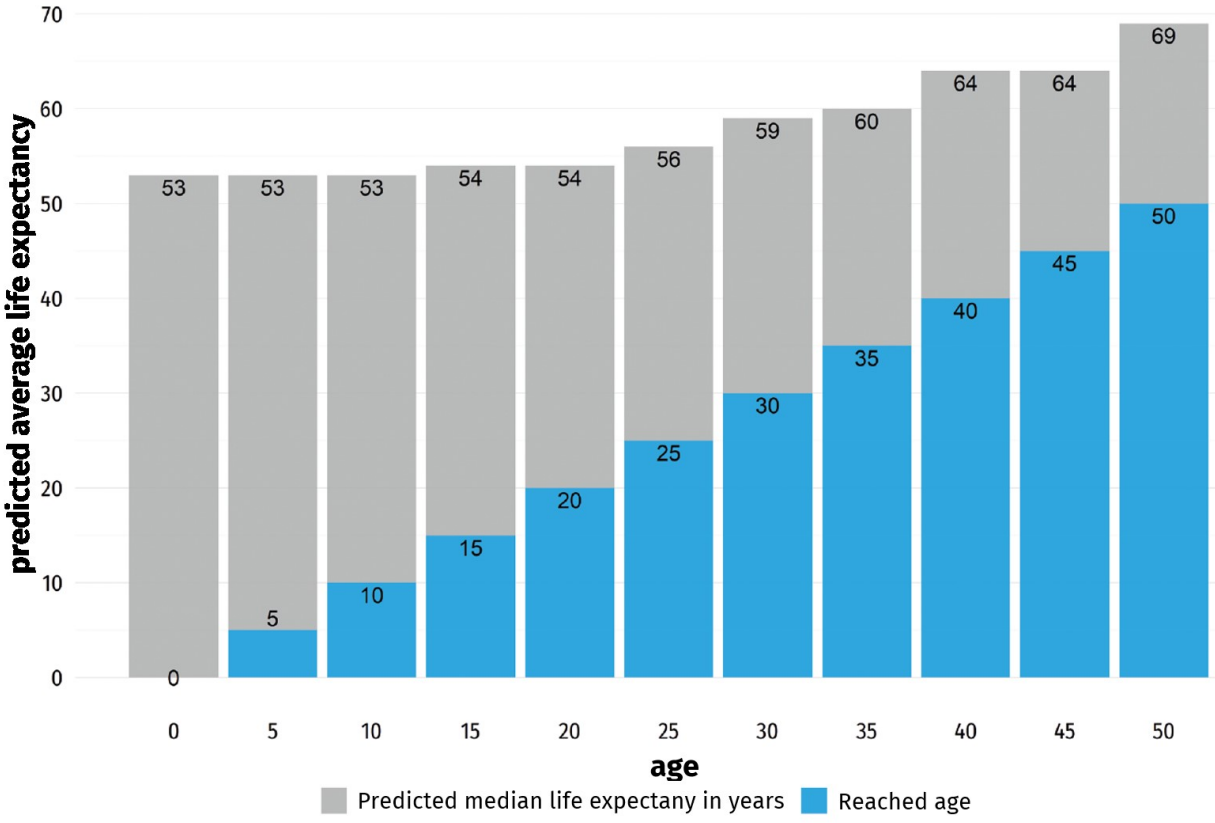

Figure 21: Predicted average life expectancy of CF patients 2013-2017

11

Structure of care

11a. Size of participants CF sites

In the reporting year 2018, 90 institutions participated in the cystic fibrosis register. 47 CF-sites cared for less than 50 patients and 43 CF-sites cared for more than 50 patients. Over 80% of the patients documented in the register are cared for in the 43 CF-sites.

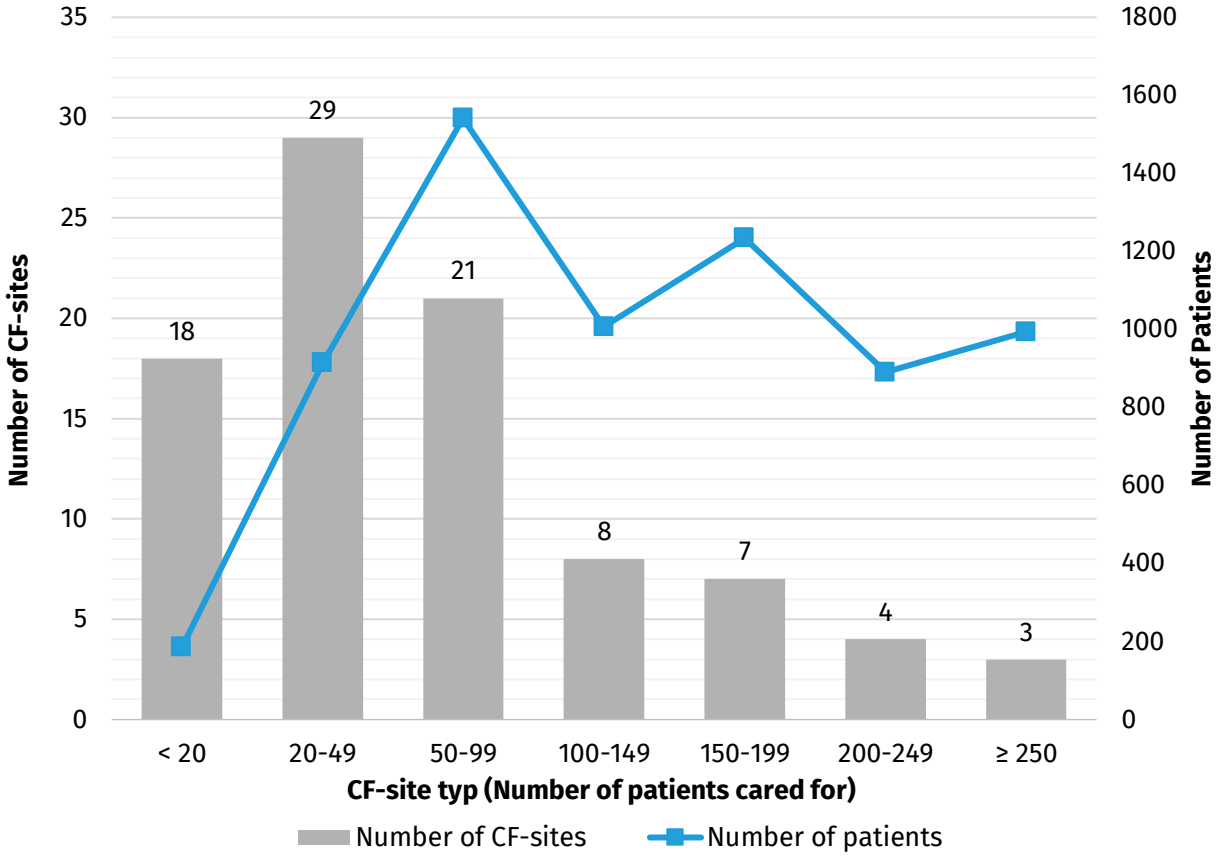

Figure 22: Number of documented patients and number of CF-sites 2018

Structure of care

11b. Outpatient care

All patients with follow-up data in 2018 (n=6340) were included in the following evaluations.

	0-5 years	6-11 years	12-17 years	18-29 years	30-39 years	≥ 40 years	Total
Physiotherapy *in the outpatient department*	68.1	70.8	70.6	51.6	42.1	43.5	56.6
Dietetic consultation *in the outpatient department*	55.1	46.5	43.8	27.4	23.1	22.3	34.7
Psychosocial support *in the outpatient department*	44.1	44.1	51.9	42.6	33.8	34.0	41.8
Imaging							
Thorax	50.4	57.6	59.2	55.2	50.6	55.5	54.7
Abdomen	63.2	62.9	61.2	47.5	50.7	46.4	54.1
Laboratory	87.9	91.7	92.2	93.9	93.6	94.6	92.6
Rehabilitation stay	7.0	8.3	8.0	5.6	9.1	9.3	7.6
Anxiety and depression screening	-	-	18.4	23.4	19.1	16.1	20.1[1]

Table 26: Outpatient care in % in the reporting year 2018

*related to CF patients 12 years and older

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Structure of care

11c. CF-relevant hospital stays

CF-relevant hospital stays	0	1	2	3	4	5+	unknown
0-5 years	66.3	18.7	5.0	1.6	1.1	0.5	6.8
6-11 years	68.3	14.7	4.9	2.1	1.3	0.9	7.8
12-17 years	56.1	18.6	6.5	3.8	2.7	2.8	9.5
18-29 years	58.3	17.4	9.0	3.6	1.8	3.2	6.8
30-39 years	65.4	15.9	7.8	5.0	1.5	1.8	2.5
≥ 40 years	66.3	18.3	7.6	3.4	1.3	1.5	1.6
Total	62.7	17.2	7.1	3.4	1.7	2.0	5.9
< 18 years	63.4	17.3	5.5	2.5	1.7	1.4	8.1
≥ 18 years	62.2	17.1	8.3	3.9	1.6	2.4	4.4

Table 27: Frequency in % of CF patients with the mentioned number of events 2018

Glossary

	Definition
ABPA (Allergic bronchopulmonary aspergillosis)	When a person develops an allergic reaction to Aspergillus fumigatus.
Anticholinergic drugs	An anticholinergic medicine has a relaxant effect on the smooth musculature and inhibits secretion.
Arthritis	A condition which causes pain and inflammations in the joints.
Arthropathy	A condition which causes pain in the joints.
Pancreas	An organ in the digestive system which produces insulin and digestive enzymes.
Beta sympathomimetics	Beta sympathomimetics are drugs Drug substanceswhich stimulate the Beta receptors of the Sympathetic nervous system.
BMI (Body Mass Index)	A measured value for the assessment of the body weight of a person in relation to its body size
Burkholderia cepacia	Burkholderia cepacia is one of a species of bacteria in the Burkholderia genus. Several of these bacteria are a potential threat to the health of people with cystic fibrosis.
CF - Cystic fibrosis	Cystic fibrosis
CFTR (Regulator of the transmembrane conductivity in case of cystic fibrosis)	A protein on the cell surface which controls the saline and water levels in a cell. The gene which causes cystic fibrosis is the blueprint for the CFTR protein. Every person has two copies of the gene for CFTR. In order for someone to be born with cystic fibrosis, both CFTR genes must be affected by a mutation causing CF.
Enzymes	Biological molecules present in the body which support complex reactions such as the digestion of foods.
FEV1 (one-second capacity)	The FEV1 (Forced Expiratory Pressure in 1 Second) is the largest-possible quantity of air which you can force out of your lungs within 1 second. The FEV1 value is a part of the lung function, and can be measured within the scope of a lung function test.
FEV1% predicted	The FEV1% is the percent value of the average FEV1 which healthy people of the same age, gender and length can achieve. Normally, this lies between 80-120%.
Gastroesophageal reflux disease	A chronic symptom of damage through stomach acid which rises up from the gastric mucosa.
Genotype	A characteristic part of the genetic structure of a cell, an organism or an individual.

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Glossary

	Definition
GLI equations	The equation of the Global Lung Initiative takes into consideration the following factors for calculation of the FEV1%: absolute FEV1, age, gender, size and ethnicity.
Haemophilus influenzae	Haemophilus influenza is a bacterium which can cause severe illness.
Haemoptysis	Coughing up blood.
Mutation	A mutation is an alteration to a gene. If both parents of a child bear a mutation which causes CF, there is a 25% chance that the child will have cystic fibrosis. There are over 1,400 different mutations of the CFTR gene.
Nose polyps	Small, sack-shaped growths caused through chronic inflammations of the nasal mucosa.
New-born screening	The new-born screening is an examination of new-born babies in order to detect congenital diseases such as cystic fibrosis at an early stage.
Non-tuberculous mycobacteria (NTM)	A mycobacteria which does not trigger tuberculosis but can still be the cause of respiratory infections. Several types are known.
Osteopenia	A less severe disease than osteoporosis, through which the mineral content of bones is reduced.
Osteoporosis	A condition in which the bones become brittle due to the loss of tissue.
Percentile	A percentile indicates where a value is relative to the rest of the data. If a value lies higher than 90% of the remaining data, we speak of the 90th percentile.
Pneumothorax	A collection of air in the cavity between the lung and the chest wall which can lead to a collapsed lung on the affected side.
Prevalence	The total number of people with this disease over the past 12 months.
Pseudomonas aeruginosa	A tenacious bacterial strain which seldom affects healthy people, but which can lead to a multitude of infections in case of a weakened immune system.
Liver cirrhosis	A chronic liver disease.