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RESEARCH ARTICLE

Comparison of Surrogate Parameters between CF-Patients in Frankfurt and Moscow (1990-2015)

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Abstract

Background: Previous studies have demonstrated that CF prognosis is dependent of three major parameters: FEV1, BMI and need of intravenous antibiotic therapy. The CF centres of Frankfurt, Germany, and Moscow, Russia, care for cystic fibrosis patients. We decided to investigate and compare both centers from 1990 to 2015. No comparable study has been published so far.

Methods: German patient data was collected from the national cystic fibrosis database "Muko.web". Missing values were extracted from the Hospital Information System. Russian patient data were taken directly from the medical records in Moscow. In a descriptive statistical analysis with Bias and RStudio the values were compared.

Results: 428 patients from Moscow (217 male, 211 female; 348 (81.3%) were *P. aeruginosa* positive) and 159 patients from Frankfurt (92 male, 67 female; 137 (86.2%) with *P. aeruginosa* positive) were compared with regard to *P. aeruginosa* positivity, BMI, FEV1 and need of intravenous antibiotic therapy. CF patients in Moscow stratified by age groups had lower BMI than CF patients in Frankfurt (age 16-18: $p = 0.003$; age 19-22: $p = 0.004$; age 23-29: $p < 0.001$; age 30-35: $p < 0.001$; age 36-66: $p = 0.024$). In a matching pairs analysis including 100 patients from Frankfurt and 100 patients from Moscow for the year 2015 FEV1 was significantly lower in Moscow patients ($p < 0.001$).

Conclusions: This study showed a significant difference in prognostic parameters between Frankfurt and Moscow in the cross-sectional analysis for the year 2015. A further study should evaluate this difference to show whether this difference will be found over a longer period of time.

Keywords

Cystic fibrosis, BMI, FEV1, Intravenous antibiotic therapy, Lung function, *P. aeruginosa*, Surrogate parameters

Introduction

Cystic fibrosis (CF) is a disease characterized by a loss of function of the cystic fibrosis transmembrane conductance regulator (CFTR) in different organs [1]. Previous work has showed that prognosis in CF is related to Body-Mass-Index (BMI), Forced Expiratory Volume in 1 second (FEV1) and need of intravenous antibiotic therapy [2], this is why these three parameters should be measured and monitored regularly. They have significant impact on survival and on quality of life of CF patients [3]. Disease progression in cystic fibrosis (CF) is marked by deterioration of a number of physiological systems [3] especially lung function is affected [2] progressively leading to pulmonary damage and in a final state to respiratory failure.

The two centers of the Pulmonology Scientific Research Institute, Moscow and the University Hospital Frankfurt (Christiane Herzog CF-Zentrum) started a collaboration starting in July 2018. Both centers care for adult CF-patients, children as well as adults.

A retrospective descriptive study was started to look for differences between patients treated in the Moscow CF center and the Frankfurt CF center from 1990 to 2015. If there was a significant and relevant difference this should be detected in a difference in the three surrogate markers of prognosis in CF: BMI [4], FEV1 [5] and the necessity of intravenous antibiotic therapy caused by exacerbations in CF [6]. BMI can be compared in stratified age classes. Higher BMI is related to better lung function test results (which improves consequently

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quality of life and survival) and in particular for underweight individuals a poorer prognosis has been reported [4]. FEV1 is the second parameter used to mark progression of CF lung disease progression and evaluate therapeutic efficacy [5]. Furthermore FEV1 is used as prognostic tool for mortality [5,7-9]. A third marker for the survival of CF patients is the need of intravenous antibiotic therapy as a result of a severe pulmonal exacerbation [6] or *P. aeruginosa* infection [10]. Exacerbations have a big consequence in terms of current morbidity as well as implications for long term morbidity and mortality [6,8]. *P. aeruginosa* presence is associated with faster rates of lung function decline in all age groups [10]. Need of intravenous antibiotic therapy consequently results in decreased survival.

No comparable study has been published so far, i.e. there has been no published comparative descriptive study comparing CF patients in different settings in the past.

Materials and Methods

German patient data

German patient data were collected from the German national CF registry "muko.web" [11]. This registry was started 1995 under the name "Qualitätssicherung Mukoviszidose" has been renamed "muko.web". In the year 2015 ninety German CF centers took part in data gathering within Muko.web describing in much detail 5331 patients (median age 20; 56.5% adults; 51.8% men; 80 died in 2015; median dying age 32) [11]. Data collected from muko.web for the study were height, weight, BMI, FEV1, Forced Vital Capacity (FVC), year of birth, year of death, gender and *P. aeruginosa* presence. In addition to this date of diagnosis of *P. aeruginosa* infection of CF-patients in Frankfurt from 1990 to 2015 were retrieved. These data were anonymized and gathered into an Excel table. Missing values - in particular those describing the utilization of intravenous antibiotic therapy (not listed in muko.web) - were completed with data from the Hospital Medical record Information System (Orbis, Agfa) of the Frankfurt University Hospital. German patients were coded with the letter "f" and were associated to group 01. They received a three-digit numerical code "XXX".

Russian patient data

Russian patient data were collected directly from the medical files of the Pulmonology Scientific Research Institute, Moscow of the FMBA (Federal Medical-Biological Agency) of Russian Federation. Collected data were anonymized and regrouped in the same standardized table as in Frankfurt. Russian patients were coded with the letter "m" and were associated to group 02. In the same way as in Frankfurt they received a three-digit numerical code "XXX".

Grouping of data

With this anonymized code data of both centers were aggregated in one data table. Gender information was coded with 01 for male patients and 02 for female patients. Body weight was expressed in kg (kilograms), body height in cm (centimeters), FEV1 in mL (milliliters), FVC in mL (milliliters). The presence of *P. aeruginosa* was coded with 01, the absence of *P. aeruginosa* with 02. Necessity of intravenous antibiotic treatment received the code 01 (02 coded not necessary intravenous antibiotic treatment).

Data analysis with Bias and RStudio

The complete data were biometrically analyzed with the program "Bias" [12]. After a descriptive approach of complete data, differences in BMI and FEV1 values were observed. Exemplarily BMI in the two centers was compared for 2015 after separating the sample in age classes [13,14]. FEV1 is an inconstant value, as it depends on age, height and sex category [15,16]. To compare FEV1 between both centers in 2015 a program was written in Rcode and executed with RStudio - a statistical programming tool, which can execute Rcode and analyze statistical data. MatchIt [17] was used to create two new comparable samples. They were matched according to the parameters influencing FEV1 (height, age, sex category) [15,16]. The size of both samples was 100 patients and both samples were statistically not significant different (before matching $p < 0.001$, after matching $p = 0.484$). Afterward both new samples were compared for their FEV1 values in a new statistical biometrical analysis with "Bias" [12].

Comparison to normal population

At the end the descriptive data of the study were compared to normal population data in Germany [18] and the Russian Federation [19-21] taking in consideration epidemiological differences, which can influence CF-patients in both centers. Especially differences in BMI in both countries may have an influence on samples BMI.

Results

Description of the data range: Year of birth

The study totalized 428 (72.91%) patients from Moscow and 159 (27.09%) patients from Frankfurt, what conducted to a total of 587 analyzed patients. All of them were born in 1999 or earlier. The oldest patient of this study was born in 1949 (Figure 1).

Average [22] year of birth was 1982 for Frankfurt, 1988 for Moscow and for the total cohort 1986. Standard deviation [22] was 11.10 for Frankfurt, 6.42 for Moscow and 8.45 for total cohort. Median [22] year of birth was 1983 for Frankfurt (1st quartile 1973, 3rd quartile 1992), 1989 for Moscow (1st quartile 1985, 3rd quartile 1993) and 1988 for total cohort (1st quartile 1983, 3rd quartile 1993). Minimum in Frankfurt was 1956. In Moscow it

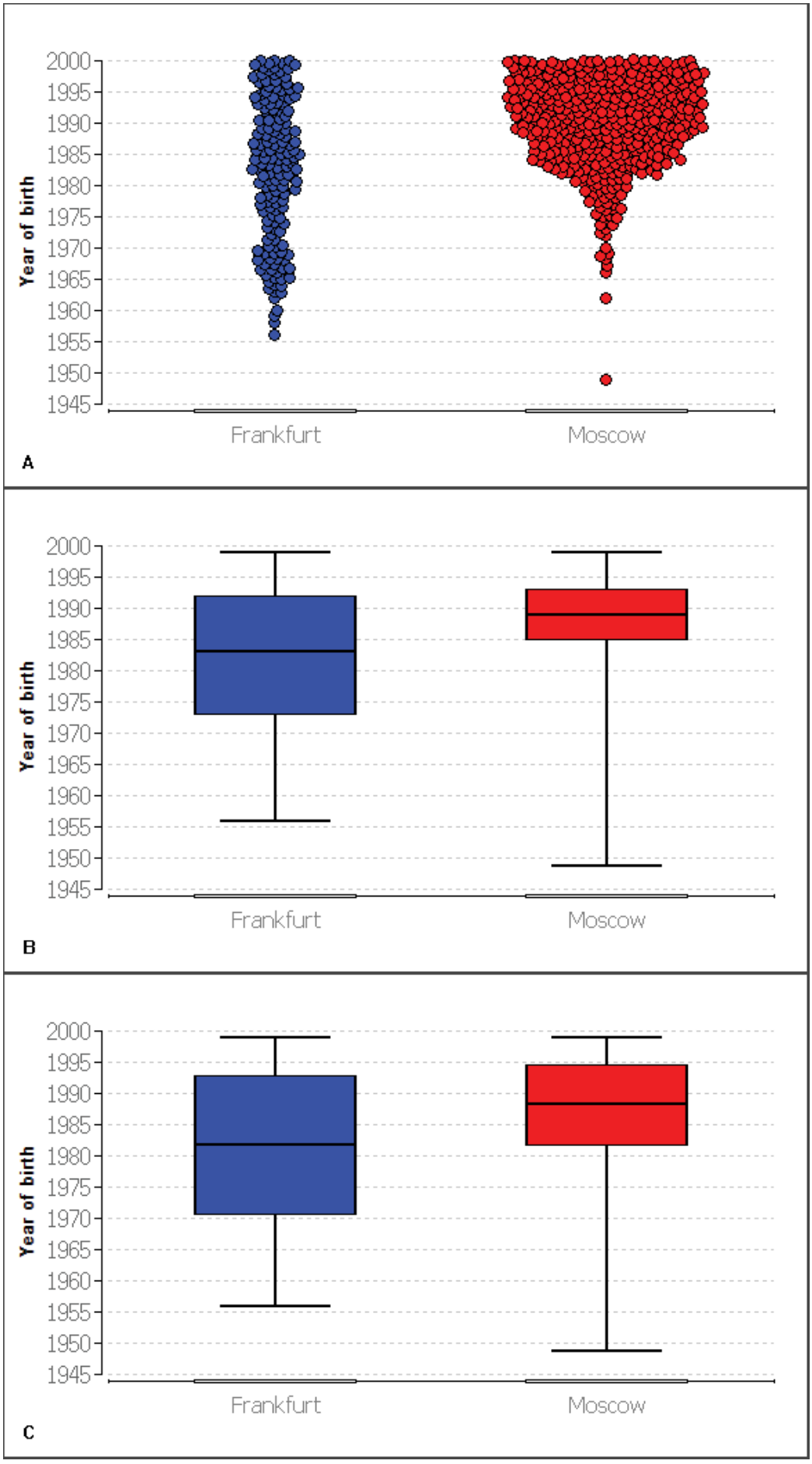

Figure 1: Differences in year of birth in both CF-populations (A) Year of birth distribution of CF-patients in both centers described in dot plots; (B) Box plot of patients year of birth representing median, first quartile and third quartile; (C) Box plot of patients year of birth representing average and standard deviation.

was 1949 (consequently 1949 for total cohort). In both centers maximum was 1999 (so same for total cohort. Finally range was 43 for Frankfurt and 50 for Moscow and total cohort.

Description of the data range: Gender distribution, *P. aeruginosa* presence and more

In Moscow 217 (50.70%) male patients and 211 (49.30%) female patients were counted, while in Frankfurt 92 (57.86%) male patients and 67 (42.14%) female patients were registered. A performed Chi-square test with Yates´s correction for continuity [22] confirms both samples were comparable (p = 0.147) for sex category distribution.

348 (81.31%) Moscow patients were infected with *P. aeruginosa* and 80 (18.69%) were not infected with this bacterium. In Frankfurt the number of *P. aeruginosa* infected patients was 137 (86.16%) while 22 CF patients were not infected (13.84%). In the same way as for the sex category distribution a Chi-square test with Yates´s correction for continuity [22] was performed (p = 0.209). Subsequently both CF-patient populations were comparable for *P. aeruginosa* infections (p = 0.209).

6 (3.77%) recorded patients died in Frankfurt (0 until 2015) and 114 (26.64%) recorded patients died in Moscow (68 (15.89%) until 2015).

Description of the data range: BMI, FEV1 and necessity of intravenous antibiotic therapy evolution over time

Data were statistically analyzed and important values were calculated and entered into Table 1. Key values of BMI, FEV1 and necessity of intravenous antibiotic therapy were examined.

Table 1: A) BMI biometrical descriptive statistic from 1990 to 2015 including number of patient data sets, average BMI, median BMI, SD (standard deviation) BMI, maximum BMI, minimum BMI, BMI range, 1st quartile BMI and 3rd quartile BMI.

Year	Number of Patient data		BMI average		BMI median	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	2	0	21.52	-	21.52	-
1991	2	1	21.54	14.49	21.54	14.49
1992	1	2	21.50	16.27	21.50	16.27
1993	2	7	20.91	16.44	20.91	15.08
1994	1	11	20.02	17.34	20.02	17.16
1995	10	7	16.66	17.36	16.11	17.16
1996	30	10	18.84	16.91	18.52	17.39
1997	35	23	19.41	17.61	19.55	17.72
1998	46	38	19.89	16.34	19.66	16.45
1999	45	39	19.97	17.33	19.13	17.65
2000	30	45	20.29	16.98	19.09	16.53
2001	14	53	19.07	16.79	18.05	16.85
2002	16	64	18.78	17.41	18.02	17.54
2003	68	78	21.43	17.42	20.85	17.55
2004	75	103	21.48	17.49	20.76	17.57
2005	13	101	20.57	18.04	20.68	18.03
2006	13	124	20.95	18.02	21.27	17.96
2007	13	160	20.51	18.11	21.10	18.13
2008	91	179	21.69	18.38	21.01	18.55
2009	84	188	22.39	18.55	21.81	18.52
2010	132	192	21.20	18.76	20.70	18.69
2011	137	199	21.40	18.71	21.14	18.47
2012	131	250	21.80	18.79	21.62	18.51
2013	130	263	21.99	18.68	21.66	18.29
2014	133	278	22.12	18.78	21.73	18.52
2015	141	301	22.24	18.74	21.63	18.59
Year	**BMI standard deviation (SD)**		**BMI maximum**		**BMI minimum**	
	Frankfurt	**Moscow**	**Frankfurt**	**Moscow**	**Frankfurt**	**Moscow**
1990	0.64	-	21.98	-	21.07	-
1991	1.13	-	22.34	14.49	20.75	14.49

1992	-	1.75	21.50	17.51	21.50	15.03
1993	1.26	2.88	21.80	20.93	20.02	13.22
1994	-	3.82	20.02	25.00	20.02	13.34
1995	2.29	2.37	20.64	22.21	13.68	15.43
1996	3.17	2.21	25.83	19.37	14.07	13.47
1997	3.18	2.49	28.22	22.77	13.71	13.34
1998	3.18	3.58	27.64	22.77	13.65	1.92
1999	3.52	2.51	31.11	22.94	14.88	12.63
2000	4.89	2.71	37.56	24.15	13.13	12.70
2001	4.02	2.69	27.76	22.76	14.60	12.40
2002	2.94	2.65	24.01	23.23	14.74	11.65
2003	3.76	2.70	33.30	23.61	13.98	11.65
2004	4.05	2.77	35.50	24.88	12.93	10.82
2005	3.22	2.76	26.35	25.86	13.73	12.02
2006	3.35	2.83	26.67	25.72	14.38	12.03
2007	3.58	2.73	24.97	25.62	13.89	12.73
2008	4.10	2.79	40.75	26.23	14.38	11.83
2009	4.41	2.78	44.29	26.03	15.34	12.80
2010	4.20	2.84	45.35	30.03	14.27	12.60
2011	4.18	2.90	45.52	31.99	14.35	12.47
2012	4.03	2.69	45.34	27.73	13.86	12.47
2013	4.04	2.80	44.47	27.73	13.86	10.85
2014	4.17	2.86	45.41	31.46	14.10	13.02
2015	4.13	2.78	46.60	31.46	14.17	11.33
Year	**BMI range**		**BMI 1st quartile**		**BMI 3rd quartile**	
	Frankfurt	**Moscow**	**Frankfurt**	**Moscow**	**Frankfurt**	**Moscow**
1990	0.91	-	-	-	-	-
1991	1.59	0.00	-	-	-	-
1992	0.00	2.48	-	-	-	-
1993	1.78	7.71	-	14.49	-	18.42
1994	0.00	11.66	-	14.22	-	19.30
1995	6.96	6.78	15.21	15.64	17.29	17.70
1996	11.76	5.90	16.51	15.35	20.88	18.85
1997	14.51	9.43	17.38	15.89	20.87	19.12
1998	13.99	20.85	17.93	14.22	21.60	18.46
1999	16.23	10.32	17.79	15.41	21.72	19.00
2000	24.43	11.45	17.59	14.81	21.15	19.23
2001	13.16	10.36	15.90	14.66	21.14	18.67
2002	9.27	11.58	16.76	15.23	21.38	18.93
2003	19.33	11.96	19.03	15.23	22.92	19.11
2004	22.57	14.06	19.23	15.21	23.00	19.47
2005	12.61	13.85	19.33	16.37	22.01	19.68
2006	12.29	13.69	19.76	15.66	22.60	19.82
2007	11.08	12.89	20.48	16.28	22.92	19.91
2008	26.37	14.40	19.58	16.47	22.80	20.09
2009	28.95	13.22	20.03	16.71	23.46	19.93
2010	31.08	17.43	18.81	16.97	22.95	20.20
2011	31.17	19.53	19.05	16.93	23.13	20.45
2012	31.48	15.27	19.34	16.86	23.29	20.45
2013	30.61	16.88	19.58	16.82	23.69	20.43
2014	31.32	18.44	19.31	16.86	23.81	20.50
2015	32.43	20.13	19.31	16.82	24.14	20.32

B) FEV1 biometrical descriptive statistic from 1990 to 2015 including number of patient data, average FEV1, median FEV1, SD (standard deviation) FEV1, maximum FEV1, minimum FEV1, FEV1 range, 1st quartile FEV1 and 3rd quartile FEV1.

Year	Number of Patient data		FEV1 average		FEV1 median	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	2	0	3800	-	3800	-
1991	2	0	3590	-	3590	-
1992	1	1	4370	2820	4370	2820
1993	2	4	3600	1280	3600	1000
1994	1	8	2550	1706.25	2550	1210
1995	6	6	2136.67	1216.67	2030	1155
1996	27	6	1825.93	1783.33	1800	1685
1997	34	19	2150.88	1998.42	2070	1640
1998	42	24	2357.62	1783.33	2090	1350
1999	44	28	2244.32	2215.00	2205	1980
2000	28	25	2512.86	2193.20	2555	2300
2001	13	30	2333.85	2019.67	2120	1955
2002	17	37	2328.82	2026.76	2090	1920
2003	66	50	2439.39	2186.00	2320	2000
2004	71	67	2447.89	2221.34	2340	2020
2005	15	73	2366.67	2296.71	2350	2030
2006	13	87	2571.54	2202.41	2450	2040
2007	13	125	2728.46	2301.36	2480	2130
2008	93	155	2354.73	2247.81	2230	2010
2009	86	171	2488.72	2299.30	2450	2220
2010	133	169	2463.91	2270.77	2270	2120
2011	137	176	2446.93	2192.33	2300	2090
2012	133	234	2437.44	2136.54	2230	2030
2013	135	251	2450.67	2120.84	2370	2020
2014	135	275	2426.81	2057.35	2310	1900
2015	145	295	2460.34	1983.12	2290	1850
Year	**FEV1 standard deviation (SD)**		**FEV1 maximum**		**FEV1 minimum**	
	Frankfurt	**Moscow**	**Frankfurt**	**Moscow**	**Frankfurt**	**Moscow**
1990	565.69	-	4200	-	3400	-
1991	1343.50	-	4540	-	2640	-
1992	-	-	4370	2820	4370	2820
1993	1173.80	671.71	4430	2280	2770	840
1994	-	1290.10	2550	4390	2550	610
1995	638.55	647.79	3320	2420	1520	600
1996	512.72	1070.49	3090	3180	920	630
1997	726.81	1160.03	3960	4060	870	610
1998	883.31	1036.85	4400	3820	1090	570
1999	821.57	1126.85	4310	5020	130	580
2000	906.30	948.37	4080	3810	900	870
2001	1041.78	1000.76	4330	4330	560	570
2002	1053.90	905.15	4540	4060	600	660
2003	1027.37	1044.13	5820	4510	500	600
2004	908.67	1063.67	4870	4790	570	480
2005	1074.40	1141.05	4530	6490	920	460
2006	930.45	1036.96	4530	5980	960	610
2007	1053.31	1043.37	4590	5650	1340	510

2008	971.57	1114.60	5030	5870	580	380
2009	1055.56	1073.32	5440	6240	560	480
2010	1036.99	981.22	5390	5390	710	730
2011	1028.96	1036.40	5440	5080	650	420
2012	1023.65	1036.54	5130	6420	580	450
2013	1015.53	1034.53	5300	6400	690	500
2014	1042.62	990.51	5370	5130	730	192
2015	1112.38	985.01	5410	5220	600	520
Year	**FEV1 range**		**FEV1 1st quartile**		**FEV1 3rd quartile**	
	Frankfurt	**Moscow**	**Frankfurt**	**Moscow**	**Frankfurt**	**Moscow**
1990	800	-	-	-	-	-
1991	1900	-	-	-	-	-
1992	0	0	-	2820	-	2820
1993	1660	1440	-	930	-	1350
1994	0	3780	-	870	-	1972.5
1995	1800	1820	1755	807.5	2200	1247.5
1996	2170	2550	1515	892.5	2060	2590
1997	3090	3450	1720	1090	2517.5	2975
1998	3310	3250	1772.5	975	2897.5	2472.5
1999	4180	4440	1775	1357.5	2607.5	3085
2000	3180	2940	1760	1230	3402.5	2740
2001	3770	3760	1520	1135	3000	2655
2002	3940	3400	1600	1280	3090	2540
2003	5320	3910	1755	1262.5	3157.5	2807.5
2004	4300	4310	1805	1405	2915	2865
2005	3610	6030	1805	1540	2790	2710
2006	3570	5370	2030	1500	2870	2695
2007	3250	5140	1920	1680	3440	2840
2008	4450	5490	1670	1370	2940	2985
2009	4880	5760	1732.5	1455	2980	3045
2010	4680	4660	1690	1560	2980	2970
2011	4790	4660	1680	1355	2960	2890
2012	4550	5970	1670	1332.5	3060	2820
2013	4610	5900	1690	1315	2975	2730
2014	4640	4938	1690	1230	2895	2785
2015	4810	4700	1600	1245	3280	2585

C) Biometrical descriptive statistical analysis of necessity of intravenous antibiotic therapy from 1990 to 2015 including number of patient data, number of necessity of intravenous antibiotic therapy and percentage of necessity of intravenous antibiotic therapy.

Year	**Number of Patient data**		**Necessity of intravenous antibiotic therapy**	
	Frankfurt	**Moscow**	**Frankfurt**	**Moscow**
1990	24	1	1	0
1991	24	2	1	0
1992	25	3	1	1
1993	26	9	1	2
1994	26	15	1	3
1995	27	12	3	4
1996	27	15	2	4
1997	27	26	2	8
1998	30	43	6	15

1999	31	44	6	18
2000	33	54	7	20
2001	36	61	10	19
2002	41	83	21	26
2003	48	90	25	31
2004	58	111	32	44
2005	63	118	27	46
2006	66	147	24	64
2007	69	180	32	79
2008	90	209	43	99
2009	98	201	35	97
2010	118	209	47	100
2011	130	222	49	105
2012	130	256	48	130
2013	139	270	52	143
2014	142	274	57	167
2015	148	295	58	191

Year	Percentage of necessity of intravenous antibiotic therapy	
	Frankfurt	**Moscow**
1990	4.17	0.00
1991	4.17	0.00
1992	4.00	33.33
1993	3.85	22.22
1994	3.85	20.00
1995	11.11	33.33
1996	7.41	26.67
1997	7.41	30.77
1998	20.00	34.88
1999	19.35	40.91
2000	21.21	37.04
2001	27.78	31.15
2002	51.22	31.33
2003	52.08	34.44
2004	55.17	39.64
2005	42.86	38.98
2006	36.36	43.54
2007	46.38	43.89
2008	47.78	47.37
2009	35.71	48.26
2010	39.83	47.85
2011	37.69	47.30
2012	36.92	50.78
2013	37.41	52.96
2014	40.14	60.95
2015	39.19	64.75

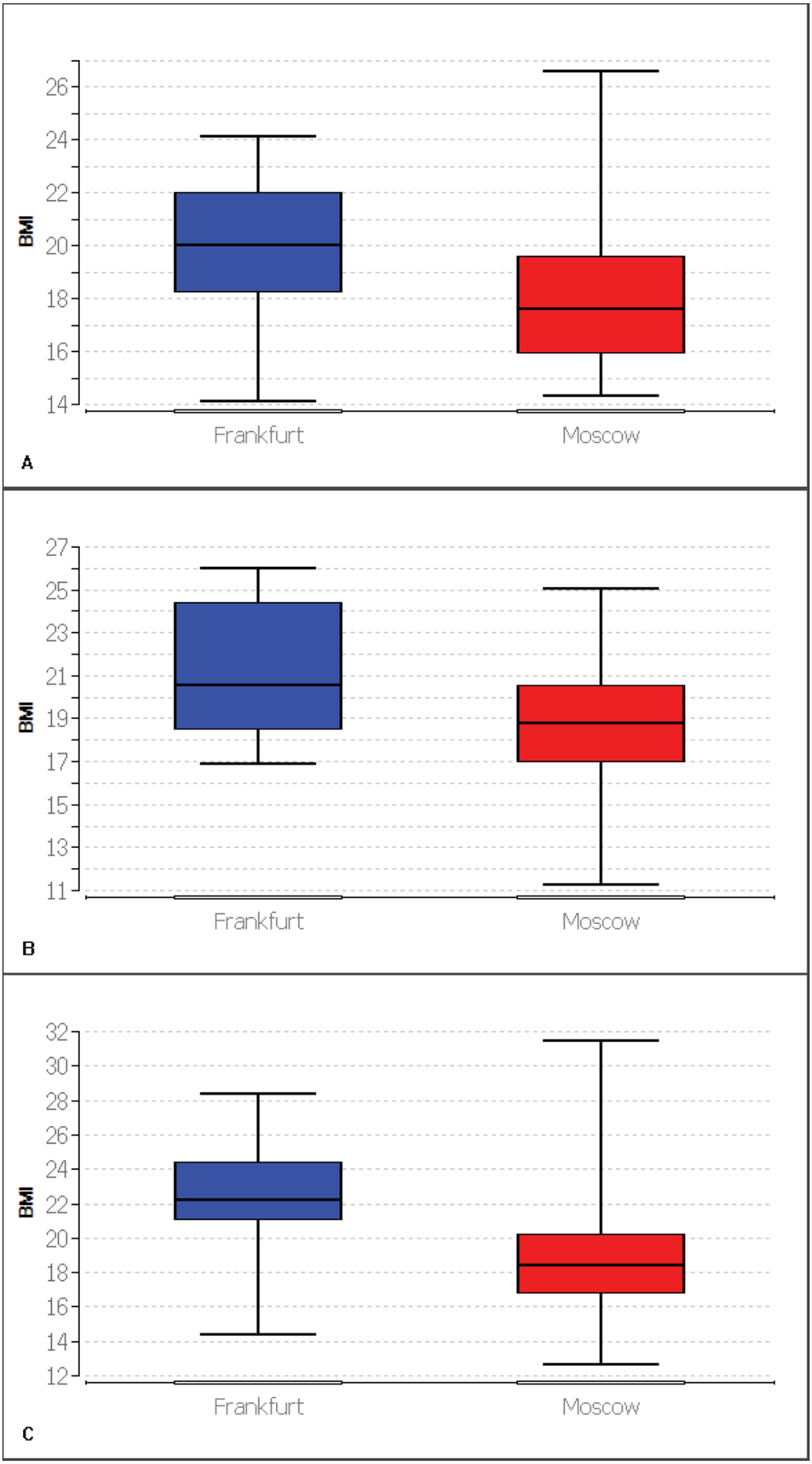

Figure 2: Box plots representing BMI comparison of patients for 2015 with median, first quartile and third quartile (A) Patients aged 16 to 18 years (Average BMI: Frankfurt (n = 12): 19.95; Moscow (n = 25): 17.90); (B) Patients aged 19 to 22 years (Average BMI: Frankfurt (n = 19): 20.87; Moscow (n = 76): 18.75); (C) Patients aged 23 to 29 years (Average BMI: Frankfurt (n = 25): 22.59; Moscow (n = 139): 18.66).

Data were statistically analyzed and values were calculated and entered into Table 1. Key values of BMI, FEV1 and necessity of intravenous antibiotic therapy were examined. In summary the parameters in Table 1 are mostly better for Frankfurt patients than for Moscow patients. From 1990 to 1995 there were not sufficient data and consequently values and results cannot be considered to be representative. FEV1 values have to corrected by height, age and sex category [15,16], therefore, they are not directly comparable.

Statistical BMI comparison of both CF populations in 2015

To evaluate if there was a significant statistical BMI difference between patients in Frankfurt and Moscow year 2015 was analyzed exemplarily. Patients were categorized in age groups (Figure 2 and Figure 3).

In 2015 Moscow CF patients stratified by age groups had statistically significant lower BMI than Frankfurt CF patients in all age groups (age 16-18: $p = 0.003$; age 19-22: $p = 0.004$; age 23-29: $p < 0.001$; age 30-35: $p < 0.001$; age 36-66: $p = 0.024$) [22,23-25].

Statistical FEV1 comparison of matched samples in 2015

To compare FEV1 in both centers a program run with RStudio [17] allowed isolation of two matched samples by height (before matching $p = 0.028$, after matching $p = 0.876$), age (before matching $p < 0.001$, after matching $p = 0.484$) and sex category (before matching $p = 0.088$, after matching $p = 0.258$) for 2015. Both included 100 patients (first sample with 100 Frankfurt patients and second sample with 100 Moscow patients) and were comparable after matching. Statistical analysis showed FEV1 was significantly lower for Moscow CF-patients ($p < 0.001$) than for Frankfurt CF-patients in 2015 (Table 2), (Figure 4).

Discussion

Summary

Data described both CF-populations in Frankfurt and

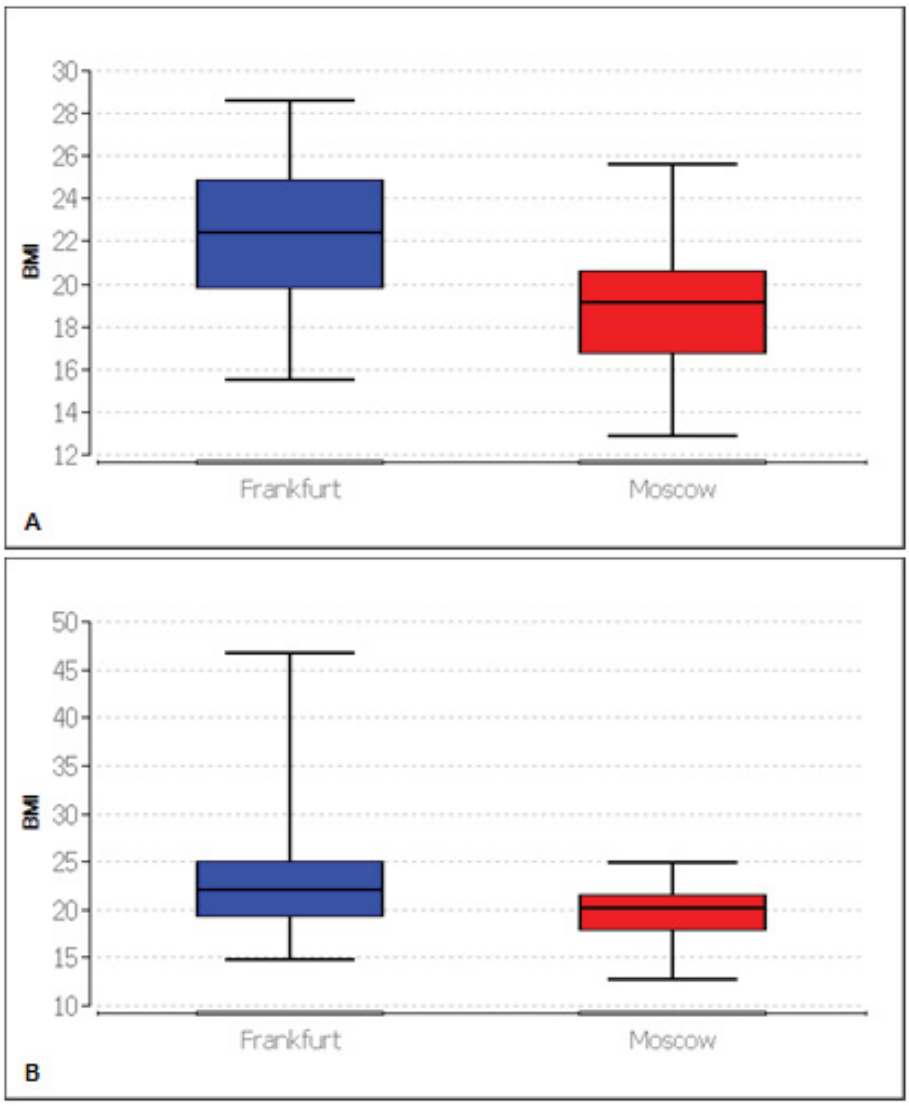

Figure 3: Box plots representing BMI comparison of patients for 2015 with median, first quartile and third quartile (A) Patients aged 30 to 35 years (Average BMI: Frankfurt (n = 29): 22.27; Moscow (n = 44): 18.97); (B) Patients older than 35 years (Average BMI: Frankfurt (n = 56): 23.03; Moscow (n = 17): 19.93).

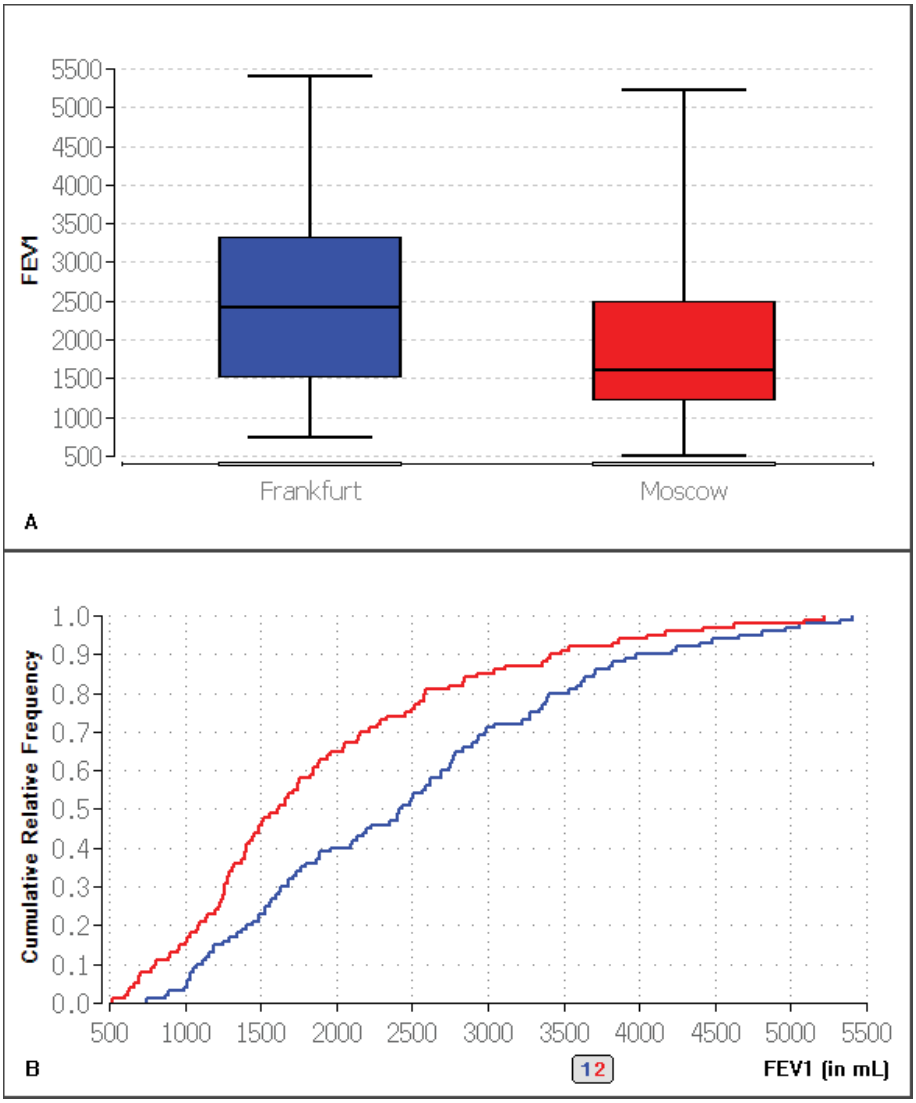

Figure 4: A) Box plot representing FEV1 comparison of both samples for 2015 with median, first quartile and third quartile; B) Empirical distribution function of FEV1 in both samples (blue = Frankfurt, red = Moscow) for 2015.

Table 2: Biometrical statistic analysis of FEV1 in 2015 for both samples (n = 100 CF-patients in Frankfurt and n = 100 CF-patients in Moscow). Average, median, SD, maximum, minimum, range, first quartile and third quartile are higher in Frankfurt than in Moscow.

FEV1	Average	Median	SD	Maximum	Minimum	Range	1st quartile	3rd quartile
Frankfurt	2497.90	2420.00	1143.19	5410.00	750.00	4660.00	1537.50	3325.00
Moscow	1908.70	1615.00	1044.80	5220.00	520.00	4700.00	1222.50	2487.50

Moscow. At first glance values of BMI, FEV1 and the necessity of intravenous antibiotic therapy were better in Frankfurt than in Moscow. An evaluation of both CF-populations for 2015 revealed BMI was significantly higher in Frankfurt, than in Moscow. A high BMI is a positive predictor for a better outcome [26,27] and decreased mortality [26]. Epidemiological analysis of normal German [18] and Russian [19-21] population didn´t explain this severe gap (referred to 3.6.). In the same way both FEV1 populations of 2015 obtained with the R-program to get comparable samples showed Frankfurt CF-patients have a better FEV1 than Moscow CF-patients. A better FEV1 is associated with a better outcome [26] and a lower mortality. Subsequently these data indicate Frankfurt patients should have a better outcome than Moscow patients.

Comparison with BMI and FEV1 of normal population

At first we had to analyze epidemiological available data of normal population to see if both are reasonably comparable. Latest data from the German federal office of statistics [18] shows a mean BMI of 26.0 for German population in 2017. Russian data [19-21] are not equally detailed and latest data was published in 2014. Mean BMI in the Russian population was 26.5. In the same year mean BMI was 26.3 in Germany, this might mean that the Russian population has a higher mean BMI than the German population, however both populations can be considered comparable. Consequently a possible gap

in BMI in both CF-populations (referred to 3.4.) cannot be explained by epidemiological data of the normal population.

A comparison of FEV1% between Germany and the Russian Federation [28] shows a difference for patients categorized in age groups. Average and mean values seem higher in Germany for children and for adults. According to ECFSPR annual report of 2017 [28] the FEV1% of Germany and the Russian Federation are different. German data seem to resemble the pooled data very closely, while the Russian data seem to be lower than pooled data and German data. This is the reason why we expected differences between both centers we wanted to analyze.

Limitations of the study

The data quality of our study should be discussed. First of all, it should be mentioned that data were not available from every patient every year. This is why the significance of the data should be nuanced. As an example, in 2015 for the entire cohort, only 486 out of 587 entries (82.79%) were found for the BMI, only 440 out of 587 (74.96%) entries were found for FEV1 and only 492 out of 587 (83.82%) entries were found for intravenous antibiotic therapy. This shows that a significant amount of data is missing and that the quality of the data is negatively affected.

Moreover, the data was collected on one hand by doctors and clinic employees, which makes human bias in the data collection possible. On the other hand, this clinically collected data is entered manually into the computer system, which makes further errors possible and can explain missing data.

Deviations due to anomalies were also found in the patient's follow-up data. These have also affected the quality of the data and thus reduced the representativeness of the data.

Possible explanation for the observed differences

In our study we could observe the Russian cohort is significantly younger than the German cohort. Average age was 33.57 for Frankfurt, 25.59 for Moscow and for the total cohort 28.14. According to ECFSPR in 2017 mean average age was 22.4 [28] years in Germany and 12.4 [28] years in Russian Federation what confirms our results.

In Moscow 217 (50.70%) male patients and 211 (49.30%) female patients were counted, while in Frankfurt 92 (57.86%) male patients and 67 (42.14%) female patients were registered. According to ECFSPR in 2017 in Germany around 52% were male patients and 48% were female. In Russian Federation the percentage was similar with about 51% male patients and 49% female patients [28]. These results were comparable with our study for Moscow. In Frankfurt the relative amount of male patients was higher than the German average. The observed gender gap could have influenced our results.

According to the number of death patient totalized in our study, there were less deaths in Frankfurt than in Moscow. This can be partially explained by new therapies [29], a better organization [30] and a medicine that becomes more and more detailed and precise due to the economic possibilities and the research. This means that German patients are in a transition phase, where life expectancy increases. Patients in Russia yet are not in this phase. This may be linked to a possible delay in the use of more modern equipment and therapies, as well as probably lower or unevenly distributed financial means.

Moreover the economic structures are different between both countries as well as the regional structures of Frankfurt and Moscow. Russia evaluated recently with the independence from the Soviet Union in 1991 and inherited an extensive centralized system. In 1993 a mandatory health insurance (MHI) was introduced to open up an earmarked stream of funding for health care, but faced lots of fiscal constraints [31]. In Germany, the health system is build up in a different way. The state is organized federally and multiple adapted health care centers were created. This was also reflected in CF management. Since 1995, the German Cystic Fibrosis Quality Assessment project has collected demographic data and outcome parameters, what aims to develop tools for quality management and improve health care [32]. This could also partly explain our results, but has to be confirmed in further studies, where economical, management and organization can be monitored.

Important and new aspect of our study

Our study is the first one comparing CF patients between both centers of Frankfurt and Moscow. It has confirmed expected differences between surrogate parameters of prognosis in CF patients of both centers. It opens new ways to research possible causes of these gaps. Our results permit to evaluate differences in therapy schemes and the use of various CF medications, in particular CFTR modulator therapies in further studies. Moreover our results show that the necessity of intravenous antibiotic treatment has also to be reexamined. The observed better results in Frankfurt for intravenous therapies in CF patients have to be proved statistically. The relation between the necessity of intravenous antibiotic therapy and a worse outcome for CF-patients has to be discussed. A study published in 2015 questioned the link between both and put other antibiotic treatments (oral therapy or inhaled therapy) on the same acting level [33].

Furthermore, we showed the reasons of these gaps in surrogate markers for CF prognosis have to be investigated. One possible cause could be a possible

difference in delta F508 mutation or other CF-specific gene mutation distribution [1]. Moreover epidemiologic reasons should be regarded in a larger scale and also compared and evaluated in another study. The socioeconomic differences between both countries should also be taken in consideration.

Our study indicates in particular that different types of drugs, modes of application, frequency of application, treatment regimens and the availability of medication could play a role in CF prognosis.

Conclusion

We have identified that Frankfurt CF patient's values for surrogate parameters of CF outcome were better than those in Moscow patients in a short time. Further studies should verify this difference on a longer lapse of time including larger data spectrum. First, this will allow establishing a hypothesis explaining this difference. Secondly, this could help to refine therapeutic approaches and to definite new recommendations.

Conflict of Interest Statement

The authors have declared that no conflict of interest exists.

Declarations of Interest

None.

Take Home Message

This study showed a significant difference in prognostic parameters between Frankfurt and Moscow in the cross-sectional analysis for the year 2015.

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