



CLINICAL CHARACTERISTICS AT HOSPITAL ADMISSION OF 5382 PATIENTS POSITIVE FOR SARS-COV-2: A SINGLE CENTER RETROSPECTIVE STUDY FROM CENTRAL NORTHERN BULGARIA

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SUMMARY

Purpose: To describe age- and sex-related differences in COVID-19 symptoms in patients admitted to emergency departments during the four waves of the pandemic in Central Northern Bulgaria

Materials and methods: Retrospective analysis of data collected from 5382 outpatients with positive result for SARS-CoV-2 by RT-PCR, admitted to 11 emergency departments in Central Northern Bulgaria, was carried out.

Results: The median age of patients was 64 years, and 60.6% of them were old adults (≥ 60 years). Overall, more patients were males (51.8%) than females (48.2%). The most frequent symptoms were fever (84.8%), dyspnea (72.3%), and cough (69.9%) without significant difference in both sexes. Less common symptoms, such as sore throat, headache, loss of taste/smell, and fatigue, were found in 1.3% to 4.0% of patients and were more prevalent in women ($p \leq 0.01$). Fever remained constant, leading symptom in all ages. The incidence of cough and dyspnoea was less in young patients and showed an increase in middle-aged and old adults. Loss of taste and smell, muscle pain and fatigue displayed the opposite trend. For the leading symptoms, the male/female ratio was >1 in all age groups, whereas for all less common symptoms, this ratio was <1 .

Conclusions: Older age, male sex and cardiovascular disease were major risk factors for COVID-19 infection. Fever, dyspnoea and cough were the core symptoms and were more prevalent in men and in adult patients. The less common symptoms were more frequent in young people and women.

Keywords: COVID-19, symptoms, age- and sex-related differences,

INTRODUCTION

On January 12, 2020, a new coronavirus was identified as a causative agent of viral pneumonia in Wuhan, China [1]. Initially, the virus was named 2019-nCoV by the World Health Organization (WHO), and later, it was renamed by the International Committee on Taxonomy of Viruses as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The disease caused by SARS-CoV-2 was named as coronavirus disease 2019 (COVID-19). The virus spread rapidly throughout the world, and on March 12, 2020, WHO declared COVID-19 a pandemic infection [3]. In Bulgaria, the first two cases of SARS-CoV-2 infection were detected on March 8, 2020 and since then, the virus spread across the country within a short period.

Early reports from Wuhan presented COVID-19 as a severe respiratory illness with fever, dry cough and atypical pneumonia [4]. Milder cases with gustatory and olfactory dysfunction and other less common symptoms were later described [5]. In-depth studies on the clinical characteristics of COVID-19 have shown differences in the clinical presentation of the infection depending on sex, age, and the presence of comorbid conditions, as well as differences related to the dominant SARS-CoV-2 variants during the pandemic [6, 7].

The aim of this retrospective study was to describe age- and sex-related differences in COVID-19 symptoms at hospital admission of SARS-CoV-2 positive patients during the four waves of the pandemic in Central Northern Bulgaria.

MATERIAL AND METHODS:

Study Design and Population

This retrospective study used data from 5382 outpatients admitted to the emergency departments of 11 sites in Central Northern Bulgaria (Pleven, Veliko Tarnovo and Lovech regions) from April 8, 2020, to May 25, 2022. Only patients with completed data of clinical symptoms and positive result for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) were included in the study.

Data collection

Patients' data during the study period were extracted from the questionnaires that were filled in at their admission to the emergency departments. The recorded anamnestic data (following the SARS-CoV-2 guidelines of the National Centre for Infectious and Parasitic Diseases) include: age and sex of the patient, date of onset of symptoms, description of symptoms, comorbidities, and epidemiological data.

Detection of SARS-CoV-2

Detection of SARS-CoV-2 genes was previously described [8]. In brief, viral RNA from nasal and oropharyngeal swab specimens was isolated with NucleoSpin Dx Virus kit (740895.50, Macherey-Nagel, Germany) or with MagCore viral nucleic acid extraction kit (MVN400-03, RBC Bioscience, Taiwan) on MagCore Plus II Automated Nucleic Acid Extractor (P26R016120120, RBC Bioscience) according to manufacturers' protocols. Essential SARS-CoV-2 genes were detected by either Genesig real-time PCR COVID-19 kit (Z-Path-COVID-19-CE, Primerdesign, UK) or GeneFinder COVID-19 Plus RealAmp kit (IFMR-45, OSANG Healthcare, Korea) following IVD-validated protocols on a CFX96 Real-time PCR machine (1854095-IVD, Bio-Rad, USA). Samples were considered positive if they showed expression of the target genes above the defined threshold. The presence of total RNA in each sample was confirmed by amplification of the internal control. All patients positive for

SARS-CoV-2 genes were included in this study.

Statistical analysis

Descriptive statistics of age were presented by means and standard deviation, and the Kolmogorov-Smirnov test was used for the normality of age distribution. Quantitative variables with a non-normal distribution were expressed by median and interquartile range. For the deviation from a normal distribution, the Mann-Whitney test was used to compare age means between groups (male/female). Categorical variables were reported as a number of cases and the percentage of groups. Fisher's exact test and Chi-square test were used to test for independence of two discrete variables.

RESULTS:

Over the pandemic, between April 8, 2020 and May 25, 2022, the median age of 5382 patients with laboratory confirmed COVID-19 infection was 64 years (IQR=51-73; Table 1). Among them, the greatest proportion belonged to the group of older patients ranging from 60 to ≥ 90 years - 3262 (60.6%), followed by the middle-aged group from 40 to 59 years - 1517 (28.2%), young adults aging 3 to 39 years - 567 (10.5%) and the smallest was the baby group from 0 to 2 years with only 36 patients (0.7%)($p=0.001$). The two most affected age groups, enclosing larger cohorts of patients, were the group 60-69 years (27.1%) and group 70-79 years (24.1%) as combine, they contained above 50% of all tested positive patients.

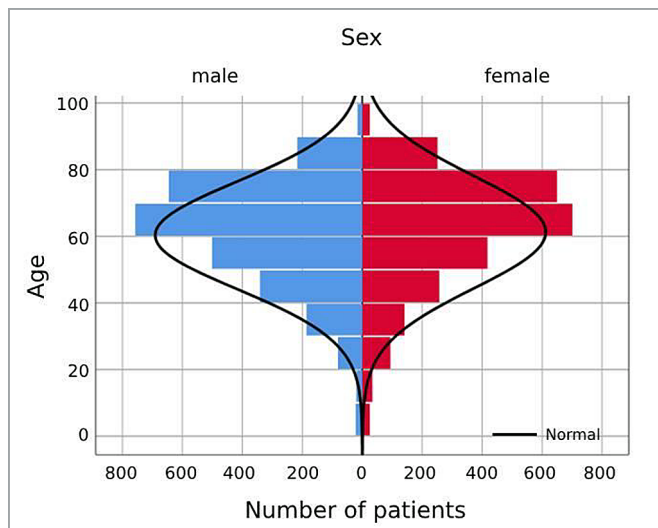
Table 1. Age and sex distribution of 5382 patients positive for SARS-CoV-2. The normality of age distribution was analyzed with the Kolmogorov-Smirnov test ($p<0.001$). The distribution of age deviates from the normal, thus the median, IQR and Man-Whitney U-test were used. Results demonstrate a significant difference in age between the sex groups, as males were younger (median age = 63) than females (median age = 64).

Age (years)	All patients -5382	Sex		P-value
		Female (n=2595)	Male (n=2787)	
Median (IQR)	64 (51-73)	64 (52-73)	63 (51-72)	$p=0.02$
0-2	36 (0.7%)	21 (0.8 %)	15 (0.5%)	
3-12	20 (0.4%)	8 (0.3 %)	12 (0.4%)	
13-19	45 (0.8%)	30 (1.1%)	15 (0.5%)	
20-29	175 (3.2%)	94 (3.6%)	81 (2.9%)	
30-39	327 (6.1%)	141 (5.4%)	186 (6.7%)	$p=0.0001$
40-49	598 (11.1%)	257 (9.9%)	341 (12.2%)	$\text{Chi}^2=30.221$
50-59	919 (17.1%)	418 (16.1%)	501 (18.0%)	Df=9
60-69	1458 (27.1%)	701 (27.0%)	757 (27.2%)	
70-79	1295 (24.1%)	650 (25.0%)	645 (23.1%)	
80-89	468 (8.7%)	251 (9.7%)	217 (7.8%)	
≥ 90	41 (0.8%)	24 (0.9%)	16 (0.6%)	

Overall, males (2787, 58%) were more prevalent than females (2595, 48.2%). Women were one year older compared to men, with a median age of 64 years (IQR=52-73) vs. 63 years (IQR=51-72), respectively ($p=0.02$, Man-Whitney U Test). There was a statistically significant difference in the distribution of males and females in all of

the age groups ($p=0.0001$, $\text{Chi}^2=30.221$, Df=9). Male patients were relatively higher in the middle-aged groups (30.2% males vs 26.0% females), while women proportion increased with age and in the group of the older patients reaches 62.6% vs. 58.7%, respectively (Man-Whitney U Test, Fig.1).

Fig. 1. Population pyramid frequency of 5382 patients by age and sex. The normality of age distribution was analyzed with the Kolmogorov-Smirnov test ($p < 0.001$). Distribution of age deviates from the normal, thus the median, IQR and Man-Whitney U-test were used. Results demonstrate a significant difference in age between the sex groups, as males were younger (median age = 63), than females (median age = 64).



A total of 2723 (50.6%) patients had pre-existing comorbidities. Single comorbidity was found in 1735 patients (32.2%), two comorbidities in 774 (14.4%), there were 169 patients with three comorbidities (3.1%) and with four and more comorbidities were 45 patients (0.8%). Cardiovascular diseases were the most prevalent comorbidity as it was reported by 2240 patients (41.6%), followed by diabetes mellitus (12.9%) and chronic pulmonary diseases (9.6%) (Table 2). The proportion of malignant diseases, chronic kidney diseases and neurological/neuromuscular diseases was small (3.0%, 2.9%, and 2.8%, respectively). Liver diseases and immunological disorders were found in less than 1% of patients. There was no statistically significant difference in the rate of comorbidities between the two sexes except for immunological disorders, which were prevalent in women ($p = 0.00004$; $OR = 3.9$).

Table 2. Comorbidities in 5382 patients positive for SARS-CoV-2. A nonparametric χ^2 test was used to determine the difference in comorbid conditions between the two sexes. Immunodeficiency disorder was found predominantly in the female population with an OR of 3.9 ($\chi^2 = 16.77$).

Comorbidity	All patients number (%)	Number of patients with medical comorbidity		M/F ratio	P-value
		Female (%)	Male (%)		
Cardiovascular diseases	2240 (41.6%)	1075 (41.4%)	1165 (41.8%)	1.08	0.78 (NS)
Diabetes mellitus	693 (12.9%)	295 (11.4%)	398 (14.3%)	1.34	0.16 (NS)
Chronic pulmonary diseases	517 (9.6%)	264 (10.2%)	253 (9.1%)	0.96	0.17 (NS)
Malignant diseases	162 (3.0%)	79 (3.0%)	83 (3.0%)	1.05	0.89 (NS)
Chronic kidney diseases	156 (2.9%)	73 (2.8%)	83 (3.0%)	1.14	0.72 (NS)
Neurological/ neuromuscular diseases	152 (2.8%)	76 (2.9%)	76 (2.7%)	1	0.65 (NS)
Liver diseases	49 (0.9%)	19 (0.7%)	30 (1.1%)	1.58	0.18 (NS)
Immunodeficiency disorder	46 (0.8%)	36 (1.4%)	10 (0.4%)	0.27	0.00004*** $\chi^2 = 16.77$, $df = 1$, $OR = 3.9$

The most frequently reported symptoms by patients on the day of sampling were fever (84.8%), dyspnoea (72.3%), and cough (69.9%) (Table 3). These three symptoms were dominant in both sexes and demonstrated no statistical difference between them. Less common symptoms, such as sore throat, headache, loss of taste/smell and fa-

tigue, were found only in 1.3-4.0% of patients and were common for women ($p \leq 0.01$). Nausea and vomiting, coryza, diarrhoea and anorexia were reported by less than 1% of patients. Interestingly, coryza was significantly higher in men ($p = 0.0025$).

Table 3. Most common symptoms reported by patients on the day of sample collection. Fisher exact test was used to assess the difference in the incidence of the most common symptoms in all patients and their distribution in the two sexes. The result is significant at $p < 0.05$. Fatigue ($p=0.0043$), loss of smell/ taste ($p=0.0198$), headache ($p=0.00001$), sore throat ($p=0.001$), nausea and vomiting ($p=0.0014$) were more common for the female population, whereas coryza ($p=0.0025$) was more prevalent in males.

Symptom	All patients (n=5382)	Female (n=2595)	Male (n=2787)	M/F ratio	P-value
Fever	4562(84.8%)	2168(83.5%)	2394(85.9%)	1.1	NS
Dyspnoea	3889(72.3%)	1826(70.4%)	2063(74.0%)	1.13	NS
Cough	3763(69.9%)	1770(68.2%)	1993(71.5%)	1.13	NS
Fatigue	216(4.0%)	126(4.8%)	90(3.2%)	0.71	0.0043
Loss of taste/smell	171(3.2%)	98(3.8%)	73(2.6%)	0.74	0.0198
Muscle pain	99(1.8%)	56(2.2%)	43(1.5%)	0.77	NS
Headache	99(1.8%)	72(2.8%)	27(1.0%)	0.38	0.00001
Sore throat	69(1.3%)	47(1.8%)	22(0.8%)	0.47	0.001
Nausea and vomiting	49(0.9%)	35(1.3%)	14(0.5%)	0.4	0.0014
Coryza	41(0.8%)	10(0.4%)	31(1.1%)	3.1	0.0025
Diarrhoea	28(0.5%)	16(0.6%)	12(0.4%)	0.75	NS
Anorexia	13(0.2%)	3(0.1%)	10(0.4%)	3.33	NS

Fever remained a constant leading symptom in all age groups (Table 4, Fig.2). The incidence of cough and dyspnoea was relatively smaller in young patients and showed a steady increase in middle-aged and old adult patients. Loss of taste and smell, muscle pain and fatigue showed the opposite trend. These symptoms had a higher frequency in young people, while their relative proportion gradually declined in those over 40 years of age. The re-

maining symptoms showed fluctuations, but there was no pronounced trend in their frequency across the different age groups. However, the only symptom that showed a statistical difference in its age distribution was dyspnoea, the frequency of which varied between 33.3% in the age group 13-19 years to 80% in the age group over 70 years ($\chi^2 = 45.8$, $df=10$, $p=0.0000015$) (Fig. 3).

Table 4. Incidence of COVID-19 symptoms by age groups. Nonparametric Chi² test was used to analyze the incidence of separate symptoms between different age groups. A significant difference was observed in the frequency of dyspnoea between the age group of 13-29 (36.95 ± 3.6) compared to age groups of 50-90 (77.36 ± 5.7); $\chi^2 = 35.95$, $Df=11$, $p=0.000085$.

Age groups	Number of patients	Fever (%)	Cough (%)	Dyspnoea (%)	Fatigue (%)	Loss of taste/smell (%)	Muscle pain (%)	Headache (%)	Sore	Nausea & vomiting (%)	Coryza (%)	Diarrhoea (%)	Anorexia (%)
									Throat (%)				
0-2	36	33 (91.7%)	28 (77.8%)	25 (64.4%)	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)	1 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3-12	20	19 (95.0%)	11 (55.0%)	10 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)
13-19	45	37 (82.2%)	23 (51.1%)	15 (33.3%)	1 (2.2%)	6 (13.3%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	2 (4.4%)	0 (0%)	0 (0%)
20-29	175	136 (77.7%)	114 (65.1%)	71 (40.6%)	9 (5.1%)	18 (10.3%)	5 (2.9%)	14 (8.0%)	11 (6.3%)	1 (0.6%)	5 (2.9%)	1 (0.6%)	0 (0%)
30-39	327	257 (78.6%)	204 (62.4%)	175 (53.5%)	22 (6.7%)	35 (10.7%)	18 (5.5%)	12 (3.7%)	13 (4.0%)	4 (1.2%)	16 (4.9%)	2 (0.6%)	0 (0%)
40-49	598	513 (85.8%)	413 (69.1%)	407 (68.1%)	23 (3.8%)	25 (4.2%)	16 (2.7%)	14 (2.3%)	11 (1.8%)	7 (1.2%)	4 (0.7%)	0 (0%)	0 (0%)
50-59	919	804 (87.5%)	653 (71.0%)	649 (70.6%)	42 (4.6%)	35 (3.8%)	22 (2.4%)	13 (1.4%)	14 (1.5%)	12 (1.3%)	5 (0.5%)	5 (0.5%)	2 (0.2%)
60-69	1459	1228 (84.2%)	1023 (70.1%)	1100 (75.4%)	60 (4.1%)	32 (2.2%)	19 (1.3%)	29 (2.0%)	9 (0.6%)	12 (0.8%)	11 (0.5%)	4 (0.7%)	4 (0.3%)
70-79	1295	1113 (85.9%)	936 (72.3%)	1021 (78.8%)	50 (3.9%)	14 (1.1%)	16 (1.2%)	12 (0.9%)	6 (0.5%)	11 (0.8%)	1 (0.1%)	8 (0.6%)	6 (0.5%)

80-89	468	391 (83.5%)	331 (70.7%)	384 (82.0%)	9 (1.9%)	6 (1.3%)	3 (0.6%)	3 (0.6%)	4 (0.8%)	2 (0.4%)	1 (0.2%)	0 (0%)	1 (0.2%)
≥90	40	31 (77.5%)	27 (67.5%)	32 (80%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
total	5382	4562	3763	3889	216	171	99	99	69	49	41	28	13

Fig. 2. Incidence of COVID-19 symptoms by age groups. Nonparametric Chi² test was used to analyze the incidence of separate symptoms between different age groups: A) fever, cough and dyspnoea; B) loss of smell/taste, muscle pain and fatigue; C) nausea and vomiting, diarrhoea and headache; D) sore throat, coryza and anorexia. A significant difference was observed in the frequency of dyspnoea between the different age groups (Chi²=35.95, Df=11, p=0.000085).

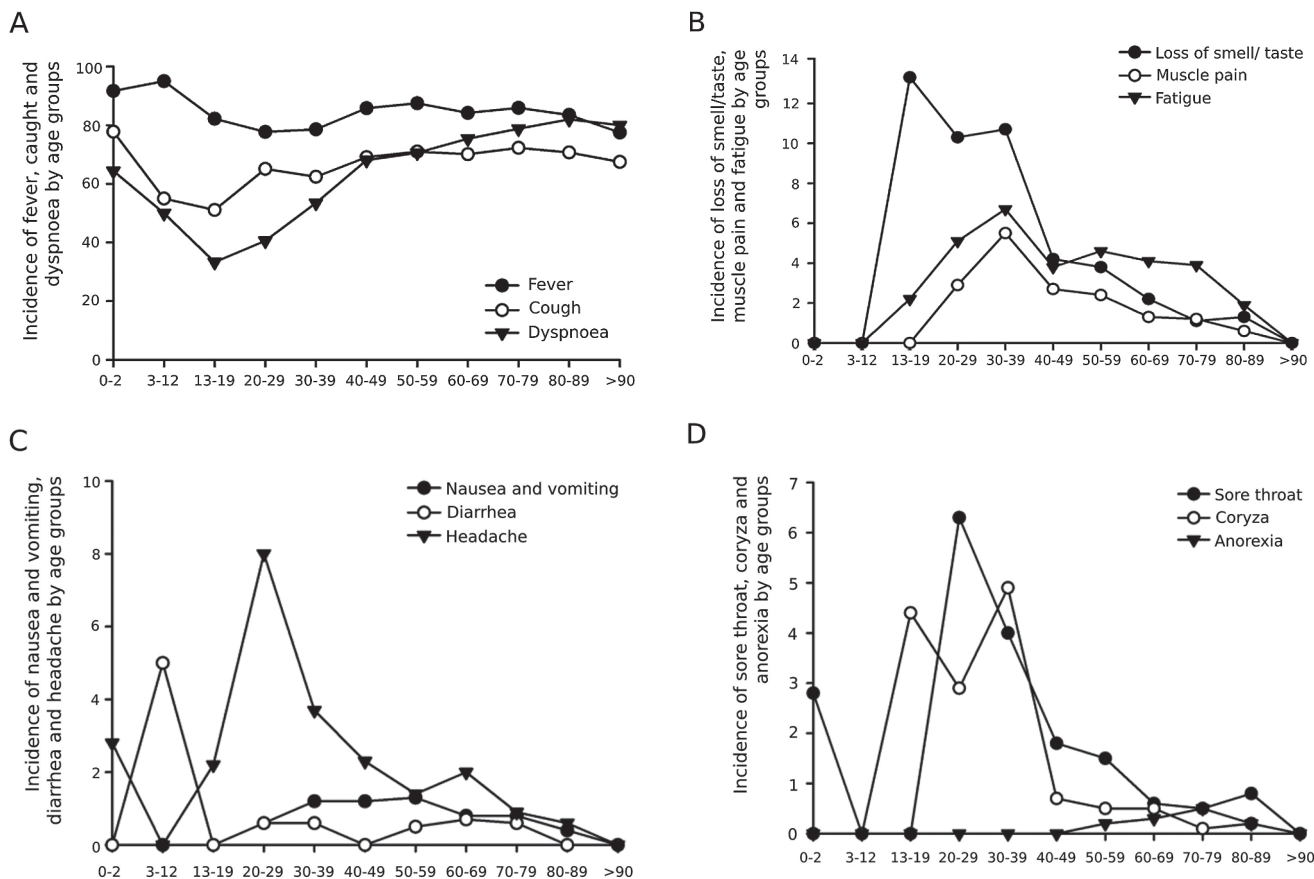


Fig. 3. Incidence of dyspnoea by age groups. A significant difference was detected in age groups of 13-29 (36.95±3.6) compared to age groups of 50-90 (77.36±5.7); Chi² =35.95, Df=11, p=0.000085.

Table 5 and Figure 4 (on 5716 p.) present the most common symptoms by sex, age group, and male/female ratio. We found a statistical difference in the frequency of fever, cough and dyspnoea between male and female patients in all age groups. For the other symptoms, there was no significant difference between sexes in different age groups. For the three leading symptoms, the male/female ratio was more than 1 in all age groups with the exception of: fever in the groups 70-79 and ≥90 years; cough in the groups 3-12 and ≥90 years; dyspnoea in the group 80-89 years. For all other less common symptoms, the male/female ratio was less than 1 with the exception of loss of smell/taste in the age group 60-69 years and muscle pain in the 70-79 years age group

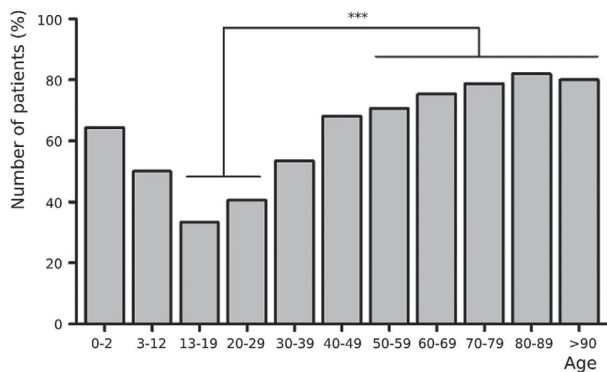


Table 5. Incidence of most common symptoms by sex and age groups, and sex-ratio. Fever (Chi2=32.65, Df=11, p=0.000311), cough (Chi2=23.03, Df=11, p=0.0106) and dyspnoea (Chi2=35.95, Df=11, p=0.000085) demonstrated a statistical difference of sex-ratios in different age groups. Male/female-ratio showed the occurrence of the most common symptoms predominantly in the male population (ratio >1) despite the age, with the exception of fever (age groups 70-79 and >90), cough (age groups 3-12 and >90) and dyspnea (age group 80-89). Less common symptoms oppositely were highly prevalent in the female population with the exception of loss of smell (age group 60-69), muscle pain (70-79), sore throat (80-89) and coryza (20-39).

Age	Sex	No.	Fever (%)	Cough (%)	Dyspnoea (%)	Loss of smell (%)	Muscle pain (%)	Fatigue (%)	Nausea & vomiting (%)	Diarrhoea (%)	Headache (%)	Sore throat (%)	Coryza (%)	Anorexia (%)
0-2	Female	21	90,5	76,2	61,9	0	0	0	0	0	4,8	4,8	0	0
	Male	15	93,3	80	80	0	0	0	0	0	0	0	0	0
	M/F ratio		1,0312	1,049	1,292									
3-12	female	8	87,5	62,5	38,5	0	0	0	0	0	0	0	0	0
	male	12	100	50	41,7	0	0	0	0	8,3	0	0	0	0
	M/F ratio		1,142	0,8	1,083									
13-19	female	30	76,7	43,3	33,3	16,7	0	3,3	0	0	0	0	0	0
	male	15	93,3	66,7	33,3	6,7	0	0	0	0	6,7	0	13,3	0
	M/F ratio		1,216	1,54	1	0,401								
20-29	female	94	73,4	58,5	37,2	10,6	3,2	6,4	1,1	0	11,7	10,6	1,1	0
	male	81	82,7	72,8	44,4	9,9	2,5	3,7	0	1,2	3,7	1,2	4,9	0
	M/F ratio		1,126	1,244	1,193	0,933	0,781	0,578			0,316	0,113	4,454	
30-39	female	141	71,6	58,2	46,8	12,1	7,1	7,1	1,4	0,7	7,1	7,1	2,8	0
	male	186	83,9	65,6	58,6	9,7	4,3	6,4	1,1	0,5	1,1	1,6	6,4	0
	M/F ratio		1,171	1,127	1,252	0,801	0,605	0,901	0,785	0,714	0,154	0,225	2,286	
40-49	female	257	83,7	67,3	62,6	6,2	3,9	5,1	1,6	0	3,5	2,3	0,8	0
	male	341	87,4	70,4	72,1	2,6	1,8	2,9	0,9	0	1,5	1,5	0,6	0
	M/F ratio		1,044	1,046	1,151	0,419	0,461	0,568	0,562	0	0,428	0,652	0,75	
50-59	female	418	85,9	69,4	66,3	5,3	3,3	6,5	2,4	0,2	2,6	1,7	0,2	0
	male	501	88,8	72,4	74,2	2,6	1,6	3	0,4	0,8	0,4	1,4	0,8	0,4
	M/F ratio		1,033	1,043	1,119	0,49	0,484	0,461	0,166	4	0,153	0,823	4	
60-69	female	701	83,7	68	74,5	2,1	1,4	5	1,3	1,1	3	0,9	0	0,1
	male	758	84,6	72	76,2	2,2	1,2	3,3	0,4	0,4	1	0,4	0,9	0,4
	M/F ratio		1,011	1,06	1,024	1,047	0,857	0,66	0,307	0,363	0,366	0,444		4
70-79	female	650	86,8	71,5	78,6	1,2	1,1	4	1,4	0,9	1,1	0,8	0,1	0,3
	male	645	85,1	73	79,1	0,9	1,4	3,7	0,3	0,3	0,8	0,1	0	0,6
	M/F ratio		0,98	1,02	1,006	0,75	1,272	0,925	0,214	0,333	0,727	0,125		2
80-89	female	251	81,7	70,5	82,5	2	0,8	3,2	0	0	0,8	0,8	0,4	0
	male	217	85,7	71	81,6	0,5	0,5	0,5	0,9	0	0,5	0,9	0	0,5
	M/F ratio		1,048	1,007	0,989	0,25	0,625	0,156			0,625	1,125		
≥90	female	24	79,2	70,8	79,2	0	0	0	0	0	0	0	0	0
	male	16	75	62,5	81,2	0	0	0	0	0	0	0	0	0
	M/F ratio		0,946	0,882	1,025									

Seven hundred and ten patients (13.2%) had only one symptom, and the remaining had combinations of 2 to 7 symptoms. Almost half (49.9%) of individuals infected with SARS-CoV-2 had three symptoms, 34.4% had two, 1.9% had four, and 0.6% had five. Combinations of six and seven symptoms were rare and were experienced by 4 and 1 patients, respectively.

Table 6 presents symptoms and combinations of symptoms for suspected COVID-19 infection. The most prevalent combination of symptoms was fever, cough and dyspnoea found in 2498 (46.4%) cases, followed by fever and dyspnoea in 874 (16.2%), and fever and cough in 544

(10.1%) (Fig.5). fever was reported as a separate symptom by 300 (5.6%) of patients, cough by 232 (3.4%), dyspnoea by 143(2.7%). The rest of the symptoms and symptom combinations appeared in less than 1% of patients. A significantly higher number of males had the most common symptom combination (fever, cough and dyspnoea) (p=0.0187), whereas females dominated in symptom combinations of fever and loss of smell/taste (p=0.02) and fever, cough and headache (p=0.0431). No significant changes were observed between males and females regarding the other symptoms and symptom combinations.

Fig. 4. Incidence of most common symptoms by sex and age groups, and sex-ratio. A) Fever ($\text{Chi}^2=32.65$, $\text{Df}=11$, $p=0.000311$), B) cough ($\text{Chi}^2=23.03$, $\text{Df}=11$, $p=0.0106$) and C) dyspnoea ($\text{Chi}^2=35.95$, $\text{Df}=11$, $p=0.000085$) demonstrated a statistical difference. D) Male/female-ratio demonstrated a predominant occurrence of most common symptoms in the male population (ratio >1) despite the age, with the exception of fever (age groups 70-79 and >90), cough (age groups 3-12 and >90) and dyspnoea (age group 80-89).

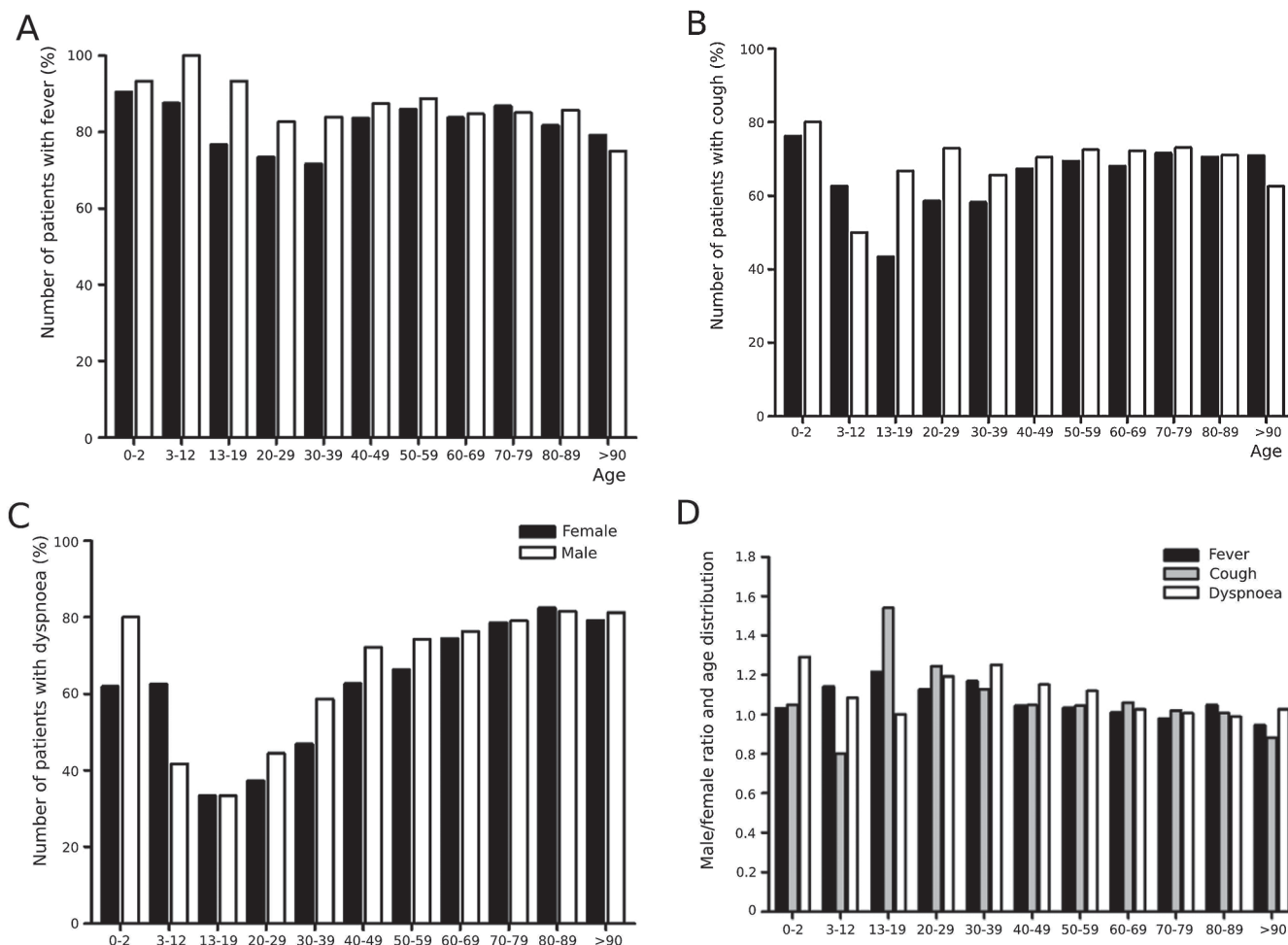
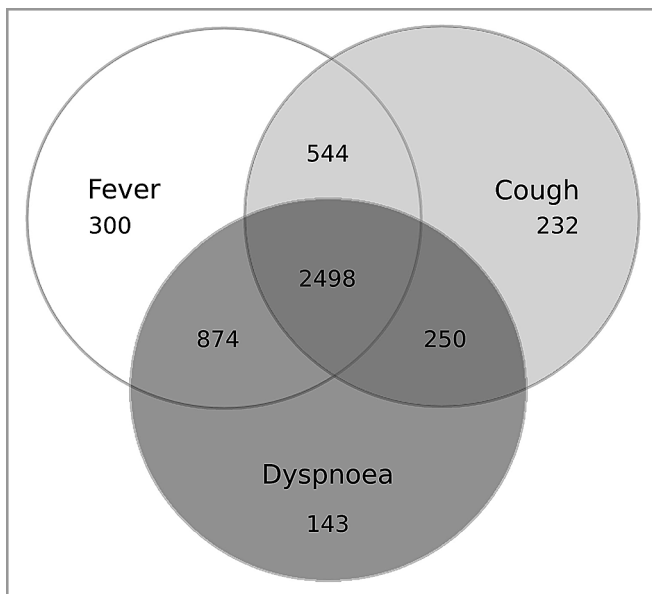


Table 6. Most prevalent symptoms and symptom combinations that were reported by patients on the day of sample collection. A significantly higher number of males had the most common symptom combination (fever/cough/dyspnoea), whereas females dominated in symptom combinations of fever/loss of smell/taste, fatigue, fever/cough/headache. No significant changes between the two sexes were found for the other symptoms and symptom combinations. The most dominant symptom combination was fever/cough/dyspnoea (46.4% of the tested population); followed by fever/dyspnoea (16.2%), fever/cough (10.1%), fever (5.6%), cough/dyspnoea (4.6%), cough (4.3%) and dyspnoea (2.7%). The rest of the symptoms and symptom combinations appeared in less than 1% of the population.

Symptoms and symptom combinations	All patients (n=5382)	Female (n=2595)	Male (n=2787)	M/F ratio	P-value
Fever, cough and dyspnoea	2498(46.4)	1133(43.7)	1365(49.0)	1.2	0.0187
Fever and dyspnoea	874(16.2)	440(17.0)	434(15.6)	0.99	NS
Fever and cough	544(10.1)	258(9.9)	286(10.3)	1.11	NS
Only fever	300(5.6)	139(5.4)	161(5.8)	1.16	NS
Cough and dyspnoea	250(4.6)	125(4.8)	125(4.5)	1	NS
Only cough	232(4.3)	114(4.4)	118(4.2)	1.04	NS
Only dyspnoea	143(2.7)	64(2.5)	79(2.8)	1.23	NS
Fever and fatigue	28(0.5)	14(0.5)	14(0.5)	1	NS
Fever, cough and fatigue	24(0.4)	12(0.5)	12(0.4)	1	NS

Fever and loss of smell/taste	22(0.4)	18(0.7)	4(0.1)	0.22	0.02
Fever, cough, dyspnea and fatigue	19(0.3)	10(0.4)	9(0.3)	0.9	NS
Fever, cough, dyspnea and loss of smell/taste	18(0.3)	6(0.2)	12(0.4)	2	NS
Only fatigue	16(0.3)	12(0.5)	4(0.1)	0.33	0.0431
Fever, cough and headache	16(0.3)	12(0.5)	4(0.1)	0.33	0.0431
Fever and headache	15(0.3)	6(0.2)	9(0.3)	1.5	NS
Cough and loss of smell/taste	15(0.3)	8(0.3)	7(0.2)	0.88	NS
Fever and sore throat	15(0.3)	6(0.2)	9(0.3)	1.5	NS
Fever and muscle pain	13(0.2)	5(0.2)	8(0.3)	1.6	NS
Cough and fatigue	13(0.2)	6(0.2)	7(0.2)	1.17	NS
Fever, cough and loss of smell/taste	10(0.2)	7(0.3)	3(0.1)	0.43	NS
Fever, cough and muscle pain	10(0.2)	8(0.3)	2(0.1)	0.25	NS

Fig. 5. Incidence of the most common symptoms and symptom combinations. The most dominant symptom combination was fever/cough/dyspnoea (46.4% of the tested population), followed by fever/dyspnoea (16.2%), fever/cough (10.1%), fever (5.6%), cough/dyspnoea (4.6%), cough (4.3%) and dyspnoea (2.7%). The rest of the symptoms and symptom combinations appeared in less than 1% of the population.



Clinical symptoms and combinations of symptoms for suspected COVID-19 infection corresponded to the WHO clinical criteria in 3328 of the cases (63.0%), to the Centers for Disease Control, United States (CDC) criteria in 4943 (91.8%), and to the European Centre for Disease Prevention and Control (ECDPC) criteria in 5322 (98.9%).

DISCUSSION:

In this retrospective study, we analyzed age- and sex-related differences in COVID-19 infection at hospital admission of SARS-CoV-2 positive patients during the four waves of the pandemic. Although multiple studies showed age related differences in severity of symptoms and mortality rate [6], conclusive data regarding age as an inde-

pendent risk factor for high incidence of COVID-19 infection are still lacking. Data from some countries show that the most affected people by SARS-CoV-2 are those of working age, whereas other countries reported that older people were more vulnerable [9].

We found an increased age-related risk of COVID-19 infection, and more than 60 % of our patients were old adults. Although SARS-CoV-2 can infect all ages, aging is a risk factor for the disease. It has been proven that during aging, the immune system changes and the susceptibility of older people to infection increases as a result of a chronic low-grade state of chronic inflammation [10].

Since the start of the pandemic, many studies have been conducted that have revealed the differences in infection susceptibility and severity between males and females. In this study, the proportion of men (51.8%) was significantly higher than that of women, but women were one year older than men. Also, the relative proportion of women was higher among elderly patients. Our results for the prevalence of men are in agreement with the data of a systematic review and meta-analysis of 57 studies with 221 195 participants [11]. The analysis demonstrates that the pooled prevalence of COVID-19 confirmed cases among men was 55.00 (51.43–56.58). It is considered that a combination of multiple biological and sex-related factors is responsible for these differences. During the last years were established some biological, immunological, and endocrine differences between males and females resulting in lower susceptibility of women to infections. Gender-specific behaviors, genetic and hormonal factors, and sex differences in some biomarkers of inflammation and expressions of angiotensin-converting enzyme 2 (ACE2) have been regarded as probable underlying factors for the observed gender differences in COVID-19 [12].

The age distribution of our patients showed significantly higher infection rates among middle-aged men than among women. This pattern reverses in the group of elders with a higher percentage of infected women compared to men. The opposite pattern was observed in Germany in the early phase of the pandemic [13]. A higher infection risk among women of working age was explained by their age- and gender-specific social behavior.

During the ongoing pandemic, multiple studies recognized the association between various pre-existing health conditions and a worse course of COVID-19 infection. Cardiovascular diseases, pulmonary diseases, diabetes, chronic kidney diseases, obesity, cancer, immunological and neurological disorders were identified as risk factors for severe COVID-19 [6]. We found pre-existing comorbidities in half of the patients with a high prevalence of cardiovascular diseases and a lower incidence of diabetes and chronic pulmonary diseases. These findings coincide with similar results from other studies [14].

The most prevalent symptoms reported by our patients were fever (84.8%), dyspnoea (72.3%) and cough (69.9%), and a combination of those symptoms was the core set in almost half of individuals. These findings are generally in agreement with data from other studies, but there was a significant difference in the frequency of symptoms. Data from the ISARIC Coronavirus Clinical Characterisation Consortium (4C) study involving 260 acute hospital sites with 59011 patients in the UK showed that cough was the most prevalent symptom (68.0%), followed by fever (66.4%) and dyspnoea (65.2%) [15]. In the meta-analysis by da Rosa Mesquita R, et al. [16] of 152 publications that included a total of 41 409 individuals from 23 countries, 26 different clinical manifestations were reported with a prevalence of fever (58.66%), cough (54.52%), dyspnoea (30.82%), malaise (29.75%), fatigue (28.16%) and sputum/secretion (25.33%). Those variations in the rate of core symptoms are probably due to differences between the studied populations. The higher percentage of dyspnoea among our patients may be the result of later seeking medical care (2-6 days after the onset of the first symptoms), as we found in our previous study [8]. Also, dyspnoea was more pronounced in the age group over 70 years, and this was related to the higher prevalence of comorbidities and more severe course of infection among elderly people.

Our findings showed statistical differences in symptoms according to age and sex. The core symptoms were more prevalent in middle-aged and older patients, while some less common symptoms, especially loss of taste and smell, muscle pain and fatigue, were more frequent in young people. The three leading symptoms were more common in men than in women, but other symptoms were more pronounced in females. Similarly, the ISARIC international study of 60 109 hospitalized symptomatic patients found a higher proportion of typical symptoms in 30 to 70 years old patients, and these symptoms were more

frequent in males than in females [7].

Olfactory and gustatory dysfunctions were reported as closely associated with COVID-19, with wide ranges in prevalence [17]. The data of meta-analysis in von Bartheld CS, et al. [5] showed chemosensory dysfunction in over 40% of the cases, and it significantly differs between populations and ethnicities. These differences may be explained by some virus mutations and genetic host factors increasing susceptibility to chemosensory dysfunctions. We found loss of smell or taste in only 3.2% of our patients with significant prevalence in women. This low prevalence may reflect, on the one hand, the fact that about three-quarters of our patients visited emergency departments during the first and second waves of the pandemic when chemosensory dysfunction was not yet expressed as a typical symptom in COVID-19. On the other hand, it may be due to the lack of recognition of these symptoms by the majority of our patients during their admission to the emergency department.

There are differences between the clinical case description of COVID-19 by WHO [18], the Centers for Disease Control - United States (CDC) [19], and the European Centre for Disease Prevention and Control (ECDC) [20]. Although each description involves the typical and less common symptoms, there are variations in the patterns of symptom combinations by WHO and CDC, while ECDC requires the presence of only one typical symptom or sudden onset of loss of smell/taste. This may explain the higher degree of coincidence of clinical symptoms reported by our patients with the case definition of COVID-19 by ECDC (98.9%) and CDC (91.8%) and low coincidence by WHO criteria (63.0%).

CONCLUSIONS:

Our results confirmed that older age, male sex and pre-existing cardiovascular disease were major risk factors for COVID-19 infection. We found an increased age-related risk with a significantly higher infection rate among older adults. The most prevalent symptoms were fever, dyspnoea and cough, and a combination of those symptoms was the core set in almost half of all patients. Our findings showed statistical differences in symptoms by age and sex. The core symptoms were more prevalent in middle-aged and older patients and were more common in men, while the less common symptoms, especially loss of taste and smell, were more frequent in young people and women.

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