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Short communication

COVID-19: comparative clinical features and outcome in 114 patients with or without pneumonia (Nord Franche-Comte Hospital, France)

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ABSTRACT

COVID-19 patients (n = 114) were included (55 patients with pneumonia (group P) and 59 without pneumonia (group NP). Patients in group P were older (69 (±17) years vs 46 (±16); $p < 0.001$) with a male predominance (58.2% vs 27.1%; $p < 0.001$). The symptoms which were statistically more frequents in patients with pneumonia were fever ≥ 38 °C (93% vs 70%; $p = 0.002$) and dyspnea (73% vs 22%; $p < 0.001$). Symptoms such as facial headache (42% vs 15%; $p = 0.001$), sore throat (39% vs 16%; $p = 0.007$), dysgeusia (61% vs 33%; $p = 0.003$), anosmia (63% vs 31%; $p = 0.001$) were statistically more frequents in patients without pneumonia.

An outbreak of pneumonia began in December 2019 in Wuhan (China), a novel coronavirus was identified as causal agent, named later the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical description from coronavirus disease 2019 (COVID-19) outbreak reveals that most of the patients have minor disease (minimal symptoms to influenza like illness) or pneumonia [1]. COVID-19 pneumonia is mainly moderate-mild, but can be severe, up to acute respiratory distress syndrome (ARDS). The aim of this study was to compare the clinical characteristics and outcome of COVID-19 patients with pneumonia and without pneumonia (i.e. parenchymal pulmonary lesions).

1. Methods

We conducted a retrospective study in NFC (*Nord Franche-Comté*) Hospital as a major French cluster of COVID-19 began on March, 1st in *Nord Franche-Comté*. Between March, 1st and March, 17th 2020, we enrolled all adult patients (≥18 years) with confirmed COVID-19 who consulted or were hospitalized in our hospital. Pregnant women, children (<18 years) and patients with dementia (unable to report functional symptoms) were excluded. Each patient (including outpatients) had physical examination (including pulmonary auscultation).

1.1. Data collection

We collected demographic characteristics, comorbidities, and characteristics of the current COVID-19: clinical features, evolution of the symptoms and outcome. Due to the beginning of the outbreak of COVID-19, we prepared a standardized questionnaire for each patient suspect of COVID-19 to help us screen their functional symptoms and the onset and duration of their symptoms. A home follow-up was recommended in our national guidelines, for patients who were not hospitalized, until they are asymptomatic for more than 48 h. Consequently, outpatients and patients who were discharged after their hospitalization were called 14 days ± 7 days after the beginning of the symptoms; in case of persistent symptoms, we contacted them again 7 days later, until they were asymptomatic to ascertain epidemiological and clinical data. For each patient, we followed the clinical evolution and outcomes at least until recovery plus 48 h.

Diagnosis was confirmed by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) on respiratory samples, for SARS-CoV-2. Viral RNA was extracted using the NucleoSpin® RNA Virus kit (Macherey-Nagel) according to the manufacturers' instructions and amplified by RT-PCR protocols developed by the Charité (E gene) [2] and the Institut Pasteur (RdRp gene) [3].

We defined two groups in this study according to the clinical and/or radiological presentation of COVID-19 patients:

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- Group Pneumonia (Group P): patients presenting with clinical (cracklings sounds on pulmonary auscultation) or para-clinical (noted by the radiologist on chest Computed Tomography –CT– scan) pulmonary parenchymal lesions.
- Group without pneumonia (Group NP); patients without COVID-19 pneumonia (no pneumonia was noted through physical and radiological examination).

1.2. Statistics

Concerning the statistical analysis, continuous variables were expressed as mean and standard deviation (SD) and compared with ANOVA test. Categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test between the two groups (patients with pneumonia and patients without pneumonia). A p-value <0.05 was considered significant. We used the SPSS v24.0® software (IBM, Armonk, NY, USA).

1.3. Ethics approval and consent to participate

Due to the retrospective nature of the study, the Ethics & Scientific Committee of *Nord Franche-Comté Hospital* determined that patient consent was required. Informed consent about study participation was officially announced verbally and noted in writing in the patient's medical record, according to national regulations for retrospective study. All patient data were anonymized prior to the analysis.

2. Results

During the study period, 114 patients were included with positive RT-PCR SARS-CoV-2 RNA. The mean age was 56.7 (±20, [19–97]) years with 57.9% female. Fifty-five patients with COVID-19 pneumonia were included in group P: 20 patients with pulmonary parenchymatous lesions on chest CT-scan and 35 patients without chest CT-scan (not performed) but with crackling sounds heard on pulmonary auscultation. In the group NP, 59 patients without pneumonia were included (no pulmonary parenchymatous lesions on CT-scan if it was realized nor any crackling sounds heard on pulmonary auscultation).

2.1. Comparaison of demographics and baseline characteristics of COVID-19 patients in the two groups (Table 1)

Patients in group P were older (the mean age was 69 (±17) years versus (vs) 46 (±16); $p < 0.001$) with a male predominance (58.2% vs 27.1%; $p < 0.001$) and a higher Charlson comorbidity index (3.2 (±2.8) vs 0.7 (±1.6); $p < 0.001$) than group NP. Forty patients in group P (72%) had underlying comorbidities. Main comorbidities were: cardiovascular disease (84%, n = 46), diabetes mellitus (26%, n = 14), chronic obstructive pulmonary disease (COPD) or asthma (16%, n = 9) and malignancy (13%, n = 7). More than two thirds of the patients in group NP (70%, n = 41) had no comorbidities. We noted also more health care worker in group NP (57.6% vs 14.5%; $p < 0.001$).

2.2. Comparison of clinical features between the two groups (Table 2)

Table 2 summarizes all functional signs (general, respiratory, neurologic, otorhinolaryngological, ocular and gastro-intestinal –GI– symptoms), physical examination and duration of symptoms in both groups.

The symptoms which were statistically more frequents in patients with pneumonia than in patients without pneumonia

Table 1
Demographics, baseline characteristics and evolution of 114 COVID-19 patients in *Nord Franche-Comte* Hospital, France, 2020.

Characteristics			Group 1 (Patients with COVID-19 pneumonia) n = 55	Group 2 (Patients without COVID-19 pneumonia) n = 59	p-(value)
Demographics and baseline characteristics of COVID-19 patients					
Age (y) (mean, extremes, SD)			68.5 ± 16.7 [32–96]	45.6 ± 16.2 [19–97]	**<0,001**
Sex (Number, %)		Male	32 (58.2)	16 (27.1)	**0,001**
Health care worker (Number, %)			8 (14.5)	34 (57.6)	**<0,001**
Current smoking (Number, %)			8 (14.5)	7 (11.9)	0,672
Comorbidities	No		15 (27.3)	41 (69.5)	**<0,001**
(Number, %)	Cardio-vascular	Hypertension	26 (47.3)	5 (8.5)	**<0,001**
	diseases	Heart failure	9 (16.4)	1 (1.7)	**0,007**
		Others[a]	9 (16.4)	5 (8.5)	0.200
	COPD[b] or asthma		9 (16.4)	5 (8.5)	0,200
	Immunosuppression[c]		2 (3.6)	2 (3.4)	0,664
	Diabetes mellitus		14 (25.5)	2 (3.4)	**0,001**
	Malignancy		7 (12.7)	1 (1.7)	**0,024**
Charlson comorbidity index (mean, extremes, SD)			3.2 ± 2.8 [0–10]	0.7 ± 1.6 [0–9]	**<0,001**
Clinical outcomes					
Hospitalization (Number, %)			52 (94.5)	9 (15.3)	**<0.001**
Duration of hospitalization (days) (mean, SD, extremes)			10.7 ± 9.9 [1–44]	3 ± 2.8 [1–10]	**0.026**
Oxygen therapy (Number, %)			44 (80)	3 (5.1)	**<0.001**
Days from illness onset to oxygenation (days) (mean, SD, extremes)			6,22 ± 4,26 [1–21]	7.66 ± 5.85 [1–12]	0.582
Patients admitted or transferred to ICU (Number, %)			12 (21.8)	0	**<0,001**
Days from conventional hospitalization to ICU admission (mean, SD, extremes)			3,90 ± 2,87 [1–11]	–	–
IMV (Number, %)			9 (16.4%)	0	**0.001**
Duration of hospitalization in ICU (mean, extremes, SD)			12,27 ± 10,03 [2–37]	–	–
Outcome (Number, %)	**Discharge**		35 (63.6)	58 (98.3)	**<0.001**
	Death		20 (36.4)	1 (1.7)	**<0.001**

[a] Defined by: cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease and thromboembolic disease.
[b] COPD: chronic obstructive pulmonary disease.
[c] Defined by: transplantation, cirrhosis, long-term steroids therapy, immunomodulators treatments.
Bold values signifies p-value < 0.05.

were fever ≥ 38 °C (93% vs 70%; $p = 0.002$) or feeling of fever (98% vs 88%; $p = 0.038$) and dyspnea (73% vs 22%; $p < 0.001$). In the other hand, the symptoms which were statistically more frequents in patients without pneumonia than in patients with pneumonia were facial headache (42% vs 15%; $p = 0.001$) defined by frontal and/or retro-orbital pain, neurologic symptoms such as dysgeusia (61% vs 33%; $p = 0.003$) and anosmia (63% vs 31%; $p = 0.001$) and otorhinolaryngological symptoms such as sore throat (39% vs 16%; $p = 0.007$), rhinorrhea (51% vs 31%; $p = 0.031$) and nasal obstruction (37% vs 6%; $p < 0.001$). No significant differences were found between the two groups with regard to any other symptom.

About physical examination, in the group P, 47 patients (86%) had crackling sounds heard on pulmonary auscultation, 2 patients had sibilant and only one had rhonchi (patient with an underlying COPD). As expected, oxygen saturation levels were lower in group P than group NP (92% (±5) vs 96% (±3); $p = 0.001$). The mean duration of all symptoms was longer in group P than in group NP (17 (±9) days vs 11 (±5); $p < 0.001$); especially for fever and cough ($p < 0.001$).

Table 2
Clinical features of 114 COVID-19 patients in *Nord Franche-Comte* Hospital, France, 2020.

Functional Signs			Group P (patients with pneumonia) n = 55	Group NP (patients without pneumonia) n = 59	p-(value)
General symptoms					
Fever (Number, (%))	Fever ≥ 38 (objective)		51 (92.7)	41 (69.5)	0.002
	Feeling of fever		54 (98.2)	52 (88.1)	**0.038**
	No fever neither feeling of fever		1 (1.8)	7 (11.9)	0.062
Highest temperature (mean, extremes, SD)			39.2 ± 0.7 [38–40]	38.6 ± 0.5 [38–40]	**<0.001**
Fatigue (Number, (%))			53 (96.4%)	54 (91.5)	0.249
Pain symptoms					
Myalgia (Number, (%))			39 (70.9)	39 (66.1)	0.581
Arthralgia (Number, (%))			39 (70.9)	36 (61)	0.266
Headache (Number, (%))		Total	25 (45.5)	51 (86.4)	**<0.001**
		Diffuse	17 (30.9)	25 (42.4)	0.205
		Facial[a]	8 (14.5)	25 (42.4)	**0.001**
		Others[b]	0	1 (1.7)	1
Respiratory symptoms					
Cough (Number, (%))			43 (78.2)	49 (83.1)	0.510
Sputum production (Number, (%))			13 (23.6)	10 (16.9)	0.374
Sneezing (Number, (%))			15 (27.3)	17 (28.8)	0.855
Chest pain (Number, (%))			18 (32.7)	15 (25.4)	0.390
Hemoptysis (Number, (%))			5 (9.1)	1 (1.7)	0.105
Dyspnea (Number, (%))			40 (72.7)	13 (22)	**<0.001**
Neurologic symptoms					
Dysgeusia (Number, (%))			18 (32.7)	36 (61)	**0.003**
Anosmia (Number, (%))			17 (30.9)	37 (62.7)	**0.001**
Otorhinolaryngological symptoms					
Tinnitus (Number, (%))			5 (9.1)	4 (6.8)	0.737
Sore throat (Number, (%))			9 (16.4)	23 (39)	**0,007**
Hearing loss (Number, (%))			3 (5.5)	2 (3.4)	0.671
Rhinorrhea (Number, (%))			17 (30.9)	30 (50.8)	**0.031**
Nasal obstruction (Number, (%))			3 (5.5)	22 (37.3)	**<0.001**
Epistaxis (Number, (%))			4 (7.3)	3 (5.1)	0.710
Ocular symptoms					
Conjunctival hyperemia (Number, (%))			2 (3.6)	3 (5.1)	1
Tearing (Number, (%))			3 (5.5)	4 (6.8)	1
Dry eyes (Number, (%))			3 (5.5)	1(1.7)	0.351
Blurred vision (Number, (%))			2 (3.6)	2 (3.4)	1
Gastro-intestinal symptoms					
Nausea (Number, (%))			19 (34.5)	18 (30.5)	0.646
Vomiting (Number, (%))			8 (14.5)	4 (6.8)	0.177
Diarrhea (Number, (%))			27 (49.1)	27 (45.8)	0.722
Abdominal pain (Number, (%))			11 (20)	15 (25.4)	0.490
Physical examination					
Respiratory rate > 22 (Number, (%))			32 (58.2)	3 (5.1)	**<0.001**
Sat 0_2 at admission (%) (mean, extremes, SD)			92 ± 4.9 [77–100]	96 ± 3.1 [90–100]	**0.001**
Duration of symptoms					
Duration of all symptoms[c] (days) (mean, extremes, SD)			17.2 ± 9.3 [5–51]	11 ± 5.4 [3–22]	**<0.001**
Duration of fever (days) (mean, extremes, SD)			10.8 ± 8.7 [0–46]	3.7 ± 3.9 [0–16]	**<0.001**
Duration of cough (days) (mean, extremes, SD)			14.6 ± 11 [0–51]	7.4 ± 5.9 [0–23]	**<0.001**
Duration of anosmia (days) (mean, extremes, SD)			10 ± 7.5 [3–21]	8.6 ± 6 [1–28]	0.559

[a] Facial headache defined by: frontal and/or retro-orbital headache.
[b] In group NP (patients without pneumonia); only one patient complained of temporal headache.
[c] Defined by the time between symptoms onset and recovery (resolution of all symptoms).
Bold values signifies p-value < 0.05.

2.3. Comparison of clinical outcomes between the two groups (Table 1)

Concerning the outcome of patients with pneumonia, 52 patients (95%) were hospitalized (vs 9 patients without pneumonia [15%], $p < 0.001$), for a mean duration of 11 days (±10). Among them, twelve patients (22%) were admitted in Intensive Care Unit (ICU) for acute respiratory failure and 9 patients (16%) were mechanically ventiled. Thirty five (59%) patients in group P had been discharged from hospital at the end of our study and 20 (36%) patients died. In contrast, only one patient died in group NP ($p < 0.001$).

3. Discussion

This report, to our knowledge, is one of the largest case series of patients with COVID-19 in France. We described a population of 114 symptomatic adults (54% inpatient [61 hospitalized patients] and 46% outpatients), infected with SARS-CoV-2.

In the literature, the mean age of patients with COVID-19 was 46 years without predominance for male [4], such as our NP group. Chen et al. showed that patients with COVID-19 pneumonia and severe presentations were older, with a mean age about 68 years, with a male dominance [5]. Seventy-two percent of patients with pneumonia had comorbidities, including cardiovascular disease, diabetes mellitus, COPD and malignancy. These comorbidities had a prevalence ≥10% in our study as in other studies [4,6,7]. Not surprisingly, patient without pneumonia were younger with a lower Charlson comorbidity index [8].

The most common symptoms at onset of illness in the group of patients with pneumonia were fever or feeling of fever and dyspnea with a significant difference when compared to the group NP. These signs were reported as the main symptoms in most cohorts with clinical description of COVID-19, especially in patients with pneumonia and severely ill patients [5,9]. However, compared with this group, patients without COVID-19 pneumonia were more likely to report symptoms such as facial headache, dysgeusia, anosmia, sore throat, rhinorrhea and nasal obstruction. In a recent published article, we suggested that neurologic symptoms in COVID-19 were more frequently described in young patients with mild and moderate presentations; furthermore, only 15 of the 54 (28%) COVID-19 patients with anosmia presented pneumonia [10].

The distribution of SARS-CoV-2 entry receptors may at least partially explain these clinical features in the two groups. However, symptoms related to the systemic inflammatory response, such as fatigue, myalgia and arthralgia are not directly linked to the distribution of viral receptors and are equally prevalent in the two groups, as observed in our study population. ACE2 protein, the functional receptor of SARS-CoV-2, is largely expressed on alveolar epithelial cells, enterocytes, and endothelial cells (including in the central nervous system) [11]. This distribution of ACE2 might reflect the observed symptoms of dyspnea, cough and crackling sound on pulmonary auscultation. Since a high expression of ACE2 receptor has recently been reported in the oral mucosa [12], the role of these receptors in the observation of frequent otorhinolaryngological symptoms during COVID-19 infection should be explored.

Patients with COVID-19 pneumonia are usually hospitalized for observation and supportive care [13] (in our study, 95% of patients in group P were hospitalized). In the group of patient without pneumonia, only 9 patients were hospitalized, mainly for extra-respiratory symptoms. Patients with COVID-19 pneumonia may become critically ill; more than a fifth of patients in group P were transferred to ICU for ARDS with a mean duration of hospitalization in ICU of 12 days and a high lethality as compared to the mortality described in China [7].

One of the limitations of our study is the limited number of patients; a bigger study would be interesting to confirm and support our results. In addition, CT-scan was not performed in all patients and the elevated number of health care workers in the group without COVID-19 pneumonia can explained the female predominance, which will not be common in general population.

In COVID-19, pneumonia affects more often older male patients with comorbidities and can worsen to respiratory failure and ARDS. COVID-19 patients without pneumonia are more often women, complaining of quite specific neurologic symptoms such as anosmia and dysgeusia. The distribution of virus entry receptors may partially support the differences in symptoms between these two presentations.

Conflict of interest statement

All authors declare no competing interests.

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References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239–42.
[2] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25:2000045.
[3] Bernard Stoecklin S, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, et al. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. Euro Surveill Bull 2020;25. 2000094.
[4] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5.
[5] Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. Linical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection 2020;48:543–51.
[6] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[7] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[8] Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect 2020;80:14–8.
[9] Lupia T, Scabini S, Mornese Pinna S, Di Perri G, De Rosa FG, Corcione S. 2019 novel coronavirus (2019-nCoV) outbreak: a new challenge. J Glob Antimicrob Resist 2020;21:22–7.
[10] Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer P-Y, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. Med Mal Infect 2020;50:436–9.
[11] Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7.
[12] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.
[13] Gandhi RT, Lynch JB, Del Rio C. Mild or moderate covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMcp2009249 [Online ahead of print.].