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CE - LETTER TO THE EDITOR

COVID-19-related symptom clustering in a primary care vs internal medicine setting

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Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome 2

Dear Editor,

Over the last year, the worldwide pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, determining coronavirus disease 2019 (COVID-19), has put a lot of pressure to the healthcare system and the scientific community. In particular, Italy has been one of the first European countries to be hit by the pandemic, and internal medicine has played a pivotal role in facing this crisis. Since then, we have gained several novel insights into COVID-19 clinical manifestations, prognosis, and treatment [1, 2]. COVID-19 clinical presentation widely varies, spacing from an asymptomatic disease course to interstitial pneumonia requiring invasive ventilation, passing through a proteiform spectrum of gastrointestinal, neurological, and systemic manifestations [1, 2]. However, although of great interest, potential differences in clinical presentation between primary care vs. hospitalised patients are still poorly characterised. In particular, possible symptoms clusterization in these two settings, that may aid the physician in predicting disease course and thus proper patient allocation, have not yet been investigated. In fact, a direct comparison of these two settings is lacking. Hence, we aimed at evaluating different clinical presentations in COVID-19 patients who were treated at home compared to those who required hospitalisation in an internal medicine ward.

We performed an exploratory, a single-centre, prospective study during the first wave of the pandemic (March–June 2020). We consecutively enrolled patients with COVID-19 admitted to our academic, internal medicine unit (San Matteo Hospital Foundation, Pavia, Italy), and a random sample of patients with COVID-19 who did not require hospital admission and who were treated by the general practitioner at home. Of note, the San Matteo Hospital immediately became one of the main COVID-19 referral centres of Northern Italy soon after the first outbreak of the disease, and, during the first wave, a standard of care for these patients had yet to be agreed on. Diagnosis of COVID-19 was always based on SARS-CoV-2 detection through nasopharyngeal swab. Total nucleic acids (DNA/RNA) were extracted from samples (200 µl) with QIAsymphony® DSP Virus/Pathogen Midi Kit (Complex 400 protocol; QIAGEN, Qiagen, Hilden, Germany). Specific real-time PCR targeting RNA-dependent RNA polymerase and E genes were used to detect the presence of SARS-CoV-2. Demographic and clinical data were either collected during the hospital stay by the treating physician (hospitalised patients), or through phone interview (primary care patients). A follow-up phone call was made after 1 month (± 1 week) since hospital discharge or recovery from active infection (as shown by a negative nasopharyngeal swab). Before study initiation, the study proponents (ADS, GRC, MVL) performed a literature review regarding all possible presenting symptoms of COVID-19, and categorised them into four groups including gastrointestinal, respiratory, neurological, and systemic symptoms. The software STATA 16 (StataCorp, College Station, TX) was used for all computations. Continuous data were described with mean and standard deviation or median and interquartile range (IQR; i.e., 25th–75th percentiles), while categorical data as counts and percent. The risk ratio for having a

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mild disease course (i.e., treated in the primary care setting), along with the 95% confidence interval (CI), was assessed. A two-sided $p < 0.05$ was considered statistically significant. The study was approved by the local ethics committee (protocol number 2020–69,543), and all patients provided written informed consent prior to study enrolment.

Overall, 100 patients were enrolled, of whom 50 were hospitalised (median age 73, IQR 58–80, 19 female) and 50 were treated at home (median age 46, IQR 33–54, 23 female). Baseline relevant characteristics of all the patients enrolled are reported in Supplementary Table 1. Patients treated in hospital received, according to the continuously

Table 1 Prevalence of clinical characteristics or symptoms experienced by COVID-19 patients according to the setting (primary care vs internal medicine ward) and risk ratio for having a mild disease (not requiring hospitalisation)

	Primary care, *n* (%)	Internal medicine ward, *n* (%)	Risk ratio (95% CI)	*p* value
Clinical characteristics				
No comorbidities	38 (80.9)	9 (19.1)	3.57 (2.12–5.98)	< 0.001
Hypertension	8 (24.2)	25 (75.8)	0.38 (0.20–0.72)	< 0.001
Diabetes mellitus	0 (0)	8 (100)	NA	0.005
Cardiopathy (any)	1 (4.8)	20 (95.2)	0.07 (0.03–0.52)	< 0.001
Multimorbidity	2 (6.3)	30 (93.7)	0.08 (0.02–0.33)	< 0.001
Use of acetylsalicylic acid	2 (15.4)	11 (84.6)	0.27 (0.07–1.01)	0.014
Use of NSAIDs	33 (91.7)	3 (8.3)	3.45 (2.26–5.24)	< 0.001
Use of anticoagulants	1 (3.4)	28 (96.6)	0.04 (0.01–0.34)	< 0.001
Polypharmacy	5 (15.2)	28 (84.8)	0.22 (0.09–0.51)	< 0.001
Gastrointestinal symptoms				
Loss of appetite	29 (51.8)	27 (48.2)	1.08 (0.72–1.61)	0.841
Epigastric pain	8 (61.5)	5 (38.5)	1.27 (0.78–2.06)	0.553
Pyrosis	9 (60.0)	6 (40.0)	1.24 (0.77–1.98)	0.576
Nausea	21 (60.0)	14 (40.0)	1.34 (0.91–1.97)	0.208
Vomiting	4 (40.0)	6 (60.0)	0.78 (0.35–1.71)	0.740
Post-prandial fullness	15 (75.0)	5 (25.0)	1.71 (1.20–2.44)	0.228
Diarrhoea	29 (61.7)	18 (38.3)	1.55 (1.04–2.32)	0.044
Bloating	15 (71.4)	6 (28.6)	1.61 (1.11–2.32)	0.047
Respiratory symptoms				
Cough	25 (51.0)	24 (49.0)	1.04 (0.70–1.54)	1.00
Stuffy nose	25 (67.6)	12 (32.4)	1.70 (1.16–2.48)	0.012
Sore throat	18 (56.3)	14 (43.7)	1.19 (0.80–1.77)	0.521
Catarrh	10 (35.7)	18 (64.3)	0.64 (0.37–1.10)	0.118
Dyspnoea	12 (30.7)	27 (69.3)	0.49 (0.29–0.82)	0.003
Chest pain	9 (36.0)	16 (64.0)	0.65 (0.37–1.15)	0.165
Neurological symptoms				
Headache	34 (80.9)	8 (19.1)	2.93 (1.88–4.56)	< 0.001
Dizziness	12 (44.4)	15 (55.6)	0.85 (0.53–1.37)	0.652
Anosmia	28 (75.7)	9 (24.3)	2.16 (1.47–3.17)	< 0.001
Ageusia	30 (69.8)	13 (30.2)	1.98 (1.32–2.97)	0.001
Systemic symptoms				
Fatigue	34 (50.7)	33 (49.3)	1.04 (0.68–1.59)	1.00
Fever (< 38 °C)	22 (44.9)	27 (55.1)	0.81 (0.54–1.21)	0.423
Fever (≥ 38 °C)	17 (47.2)	19 (52.8)	0.91 (0.60–1.39)	0.835
Myalgia	31 (68.9)	14 (31.1)	1.99 (1.31–3.01)	0.001
Significant weight loss	7 (53.9)	6 (46.1)	1.08 (0.65–1.88)	1.00
Joint pain	23 (67.7)	11 (32.3)	1.65 (1.14–2.39)	0.019
Conjunctivitis	12 (80.0)	3 (20.0)	1.78 (1.26–2.52)	0.022

NSAIDs non-steroidal anti-inflammatory drugs

evolving recommendations, antibiotics (azithromycin and/or doxycycline, piperacillin-tazobactam in most cases), hydroxychloroquine, low-molecular-weight heparin, and nutritional and oxygen support as needed. Only a minority of patients (14/50, 28.0%) received intravenous steroids, as they were not standard of care at that time. Most patients treated at home instead were only treated with paracetamol (37/50, 74.0%), while the remnants (13/50, 26.0%) also took antibiotics (azithromycin or doxycycline) and hydroxychloroquine.

Of note, hospitalised patients were significantly older, had greater body mass index, smoked more cigarettes/day, and experienced fewer symptoms compared to primary care patients. Table 1 reports the prevalence of clinical characteristics or symptoms experienced by COVID-19 patients, along with the risk ratio of mild disease course (not requiring hospitalisation), according to the setting of enrolment. The median duration of symptoms was 14 days (IQR 10–21) for primary care patients and 10 days (IQR 7–14) for hospitalized patients. As expected, patients with multimorbidity, polypharmacy, hypertension, and cardiopathy were associated with a greater risk of hospitalisation, while the absence of comorbidities and the use of non-steroidal anti-inflammatory drugs were associated with a mild disease course. Also, regarding symptoms, only dyspnoea was associated with hospitalisation. A cluster of symptoms was instead significantly associated with a mild disease course, including, among others, diarrhoea, bloating, anosmia/ageusia, conjunctivitis, and myalgia. All patients treated at home recovered from COVID-19 and none of them died, nor required hospital admission. Instead, 14 out of 50 (28.0%) hospitalized patients died during hospital stay, and four patients (8%) were transferred to the intensive care unit. At 1-month follow-up, all patients treated at home were still alive, and did not require hospital admissions. Instead, five patients (10.0%) of the hospitalised cohort died at follow-up.

The results of our exploratory study have different implications. First, the wide clinical heterogeneity of COVID-19 makes it challenging to tailor a correct patient allocation, especially when the healthcare system is put under constant pressure, and the prognostic significance of COVID-19 clinical presentation is still poorly characterised. The WHO has drafted dedicated recommendations regarding the home care for patients with COVID-19, as well as for the role of primary care in this context (https://www.who.int/publications/i). However, in both cases, only a generic recommendation for monitoring the worsening of symptoms, especially the respiratory ones, is given. According to our results, from a practical point of view, given the scarcity of healthcare resources, the presence of gastrointestinal symptoms, anosmia/ageusia, and the absence of dyspnoea seem to predict a favourable disease course, and patients experiencing these symptoms can be followed up in a primary care setting, thus reducing the bed occupancy rate. These patients, especially those of younger age and with no chronic diseases, can be reassured and should be advised not to go to the A&E to avoid the potential spread of the infection. On the other side, older and/or multimorbid patients experiencing worsening respiratory symptoms should be advised to access the A&E as early as possible, as they have a poor prognosis. Regarding possible explanations to our findings, we could speculate that the fact that patients complaining of "mucosal" symptoms, such as diarrhoea, conjunctivitis, and anosmia/ageusia have a mild disease course, seems to suggest that SARS-CoV-2 does not spread to other organs possibly due to an early immunological response sustained by mucosal secretory IgA, as it was recently shown [3]. In particular, the gastrointestinal tract may act as a barrier [4] to the so-called "SARS-CoV-2 sepsis" [5]. Accordingly, patients suffering from immunodeficiencies, especially those affecting the humoral immunity and spleen function, might be at higher risk of having severe COVID-19.

We are aware that our study has many limitations, including the small sample size, which precluded a multivariable analysis of the data, and the lack of a long-term follow-up, which was out of the scope of this paper. Also, a precise pathophysiological explanation of our findings cannot be provided. However, this is the first report of a direct comparison of these two different settings, providing background for future research and a clinical message for physicians. Indeed, further studies are needed for looking at COVID-19 symptom clustering that may help physicians in predicting the need for hospitalisation.

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Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

Ethics approval The study was approved by the local ethics committee (protocol number 2020–69543).

Human and animal rights The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent All patients provided written informed consent prior to study enrolment.

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