Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Prevalence and clinical significance of relative bradycardia at hospital admission in patients with coronavirus disease 2019 (COVID-19)

Alessandra Oliva [1, *], Cristiana Franchi [1], Maria Chiara Gatto [2], Gioacchino Galardo [3], Francesco Pugliese [4], Claudio Mastroianni [1, **]

[1] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy
[2] Department of Clinical, Internal, Anaesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Italy
[3] Medical Emergency Unit, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy
[4] Anesthaesiology and Intensive Care Group, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy

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To the Editor,

Heart rhythm disorders are increasingly reported during coronavirus virus disease 2019 (COVID-19) and the presence of relative bradycardia (RB), known as an inappropriate low heart rate (HR) in response to an increased body temperature (BT), has been reported only occasionally [1]. However, its definition varied widely among studies and little is known regarding its role in predicting clinical outcomes [1,2]. We evaluated the prevalence and clinical significance of RB at hospital admission in patients with COVID-19. From March to September 2020, we performed a retrospective single-centre study including all adult patients hospitalized at Policlinico Umberto I-Sapienza University (Rome) with confirmed COVID-19 (SARS-CoV-2 RNA detected by real-time PCR on nasopharyngeal swab). Exclusion criteria were treatment with HR-lowering agents and non-sinus rhythm at ECG. RB was defined as HR < 90 bpm and concomitant fever (BT $\geq$ 38.3°C) [1]. Median (interquartile range) and frequency with percentage were used for continuous and categorical variables. The study was approved by local ethics committee, and was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Institutional Review Board.

Over the study period, 501 patients with COVID-19 were hospitalized and 63 were further excluded due to concomitant treatment with HR-lowering agents (n = 44) or non-sinus rhythm at ECG (n = 19). In the remaining 438 subjects, median age was 63 years old (51–75), 253 (57.7%) were male and median duration of symptoms before hospital admission was 6 days (2.9–9). At admission, fever was present in 101 subjects (23%) and RB in 42 patients (41.6%) (Table 1). In subjects with RB, median HR and BT were 83.5 bpm (77–89) and 38.8°C (38.6–38.9), whereas patients without RB had median HR 110 bpm (100–115) and BT 38.4°C (38.3–38.6) (p < 0.001 and p 0.0001, respectively). Patients with RB were older (68 vs 60.5 years, p 0.019) and tended to have a shorter duration of symptoms (p 0.06) than patients without RB. Type of symptoms, comorbidities and laboratory analyses did not differ between the two groups, as well as ICU admission and in-hospital mortality. At multivariable analysis, age (p 0.025) and higher temperature (p 0.001) were associated with RB at admission.

Cardiovascular involvement during the course of SARS-CoV-2 infection has been increasingly reported [3]. However, very few data regarding RB are present, showing that age was associated with RB and that RB did not influence clinical outcomes [1,2]. Herein, we describe the prevalence and clinical features of RB at hospital admission in patients with COVID-19 and we found that it was present in 41.6% of subjects with COVID-19 and fever. RB has been associated with several non-infectious and infectious conditions such as typhoid fever, Legionnaire's disease and leptospirosis [4]. Although generally referring to a condition characterized by an inverse relationship between temperature and HR, definition of RB widely differed among studies, leading to a high variation of its prevalence [1,2]. However, irrespective from the used definitions, RB was a common finding in COVID-19. We used a stringent definition of RB and we found a slightly

* Corresponding author: Alessandra Oliva, Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy.
** Corresponding author: Claudio Mastroianni, Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy.
E-mail addresses: alessandra.oliva@uniroma1.it (A. Oliva), claudio.mastroianni@uniroma1.it (C. Mastroianni).

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Table 1
Clinical characteristics of COVID-19 patients with ($n = 42$) and without ($n = 59$) relative bradycardia at hospital admission

Characteristics	All subjects $n = 101$	Subjects with relative bradycardia $n = 42$	Subjects without relative bradycardia $n = 59$	p
Age, years, median (IQR)	63 (52–75)	68 (56–81)	60.5 (50–69)	0.019
Sex, *n*	67M, 34F	30M, 12F	37M, 22F	0.36
Duration of symptoms, days, median (IQR)	6.8 (4–10)	5 (2.8–8)	7 (4.5–10)	0.06
Body Temperature, °C, median (IQR)	38.6 (38.4–38.8)	38.8 (38.6–38.9)	38.4 (38.3–38.6)	0.0001
Heart rate, bpm, median (IQR)	98 (86–110)	83.5 (77–89)	110 (100–115)	<0.0001
PaO_2/FiO_2, median (IQR)	335 (300–414)	338 (290–433)	328 (305–385)	0.655
Severe illness[a], *n* (%)	23 (22.7%)	12 (28.5)	11 (18.6)	0.241
Laboratory analyses, median (IQR)				
Haemoglobin, g/dL	13.5 (12.5–14.5)	13.3 (12–14.3)	13.8 (12.2–14.6)	0.332
White blood cells, $\times 10^6$/L	5820 (4435–8160)	6200 (4720–8180)	5650 (4340–8150)	0.333
Neutrophils, $\times 10^6$/L	4515 (3165–6525)	4695 (3410–6240)	4060 (3030–6760)	0.475
Lymphocytes, $\times 10^6$/L	705 (550–1065)	725 (560–1300)	670 (540–1050)	0.131
N/L ratio, *n*	5.4 (3.8–8.9)	5.13 (3.23–8.64)	5.4 (3.95–9.11)	0.688
Platelets, $\times 10^9$/L	196 (156–240)	186 (143–231)	198 (164–247)	0.705
Albumin, g/dL	3.7 (3.3–4.1)	3.7 (3.3–4.1)	3.7 (3.3–4.1)	0.703
D-dimer, μg/L	783 (537–1690)	1002 (571–2115)	742 (521–1493)	0.162
C-reactive protein, mg/dL	7.7 (3.1–13.9)	7.71 (2.96–13.91)	7.71 (3.11–13.9)	0.819
Comorbidities, *n* (%)				
Diabetes mellitus	22 (21.7)	8 (19)	14 (23.7)	0.648
Hypertension	43 (42.5)	18 (42.8)	25 (42.3)	0.937
COPD	14 (13.8)	6 (14.2)	8 (13.5)	0.906
Cancer	11 (10.8)	7 (16.6)	4 (6.7)	0.282
Symptoms, *n* (%)				
Cough	60 (59.4)	21 (50)	39 (66.1)	0.104
Dyspnoea	53 (52.4)	23 (54.7)	30 (50.8)	0.692
Diarrhoea	18 (17.8)	6 (14.2)	12 (20.3)	0.433
Duration of stay in the ER, hours, median (IQR)	8 (5–11)	7.5 (5.2–10.75)	8.5 (3.75–11.5)	0.687
Therapies, *n* (%)				
Hydroxychloroquine	68 (67.3)	25 (59.5)	43 (72.8)	0.164
Azithromycin	53 (52.4)	23 (54.7)	30 (50.8)	0.435
Protease inhibitors	30 (29.7)	10 (23.8)	20 (33.8)	0.415
Tocilizumab	36 (35.6)	10 (23.8)	26 (44.0)	0.083
Corticosteroids	46 (45.5)	20 (47.6)	26 (44.0)	0.590
Enoxaparin	51 (50.4)	21 (50.0)	30 (50.8)	0.287
Outcomes, *n* (%)				
ICU admission	10 (9.9)	4 (9.5)	6 (10.1)	0.915
In-hospital mortality	16 (15.8)	7 (16.6)	9 (15.2)	0.848

Data are given as medians with interquartile ranges (IQR) or as means for continuous variables and as simple frequencies, proportions, and percentages for categorical variables. Mann–Whitney test was used for unpaired samples. Dichotomous variables were compared using Fisher or chi-squared test statistics, as appropriate. All statistical analyses were performed with STATA/IC software (StataCorp) version 15.N/L, neutrophil to lymphocyte ratio; COPD, chronic obstructive pulmonary disease; ICU, Intensive Care Unit. ER, Emergency Room.

[a] Severe illness was defined according to NIH-COVID-19 criteria as SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths/min or lung infiltrates >50% (available at https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/).

lower prevalence than Capoferri et al. [1], which might be explained by the fact that we included only data at hospital admission and not during hospitalization. Of note, patients with RB presented with a higher percentage of severe illness but received less often, albeit insignificantly, tocilizumab or hydroxychloroquine. Whether the presence of RB at admission may have been associated with a more favourable course of the disease and, therefore, may have influenced the subsequent therapeutic choices is still unknown and deserves future investigation.

Several mechanisms have been proposed for the pathogenesis of RB, including direct pathogen effect on myocardial tissue, increased vagal tone and systemic inflammation with release of cytokines, all conditions present during COVID-19 [4]. In particular, interleukin 6 plays a crucial role in the development of cytokine storm implicated in the progression of the infection and also increases vagal tone. Other possible postulated mechanisms are the impairment of autonomic control of HR caused by the toxic effect of SARS-CoV-2 on nervous system or a direct viral inhibitory effect on sinus node activity [5].

Similarly to the published studies, we confirmed that ICU admission and in-hospital mortality were not influenced by the presence of RB. However, we still do not know whether the presence of heart rhythm disorders, including RB, might have long-term cardiac sequelae.

The present report has some limitations, including its retrospective and single-centre nature. Furthermore, we were not able to report two measurements within 24 hr [1] for all the patients for the following: (a) simultaneous BT and HR were usually recorded at hospital admission and subsequent vital signs did not always include their simultaneous records, and (b) the short stay in the Emergency Room. Likewise, HR and BT were not systematically recorded during hospitalization, possibly leading to an underestimation of the real prevalence of RB. Nevertheless, our main objective was to evaluate the prevalence of RB at admission and not during hospitalization.

In conclusion, RB is a common feature of COVID-19 in patients requiring hospitalization, especially in older patients and those with the highest temperature. Further studies are warranted in order to define the exact pathogenetic mechanisms behind the development of RB and to assess whether RB at hospital admission is associated with worse outcomes.

Transparency declaration

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Author contributions

All authors have made substantial contributions to this work and have approved the final manuscript. Concept and supervision: O.A., M.C.M. Acquisition and analysis of data: F.C., G.M.C., G.G., P.F.; interpretation of data: O.A., G.M.C. Writing of the original draft: O.A.

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