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Letter to the Editor

Clinical case definition of COVID-19 and morbid obesity: Is it time to move on?

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Dear Sir,

Morbid obesity (i.e., body mass index $\geq 30\,kg/m^2$) is a well-known risk factor for severe outcomes of infectious respiratory diseases [1,2]. Interestingly, some reports on COVID-19 have suggested that morbidly obese patients may be characterized by a distinctive symptomatology, being more likely to report cough, headache and myalgia [3]. The underlying mechanisms remain unclear. In fact, obesity is associated with low-grade chronic inflammation, which impairs both innate and adaptive responses of the immune system [4]. Moreover, Angiotensin-Converting Enzyme 2 receptor (ACE2), the functional receptor for SARS-CoV-2, is upregulated in obese patients [3,4]. As a result, the World Health Organization's (WHO) clinical criteria defining "*probable cases*" of COVID-19 may be somewhat inappropriate in morbidly obese patients [5]. A clinical definition was introduced by WHO to address settings characterized by limited diagnostic resources, and includes all patients with a previous contact with another probable or confirmed case, or linked to a COVID-19 cluster, who had experienced since February 24, 2020 at least one episode of anosmia/dysgeusia or had chest imaging suggestive of COVID-19, or an association of rapid onset fever (self-measured temperature $\geq 37.5\,^{\circ}C$) and cough, or an association of any three or more of the following signs and symptoms: fever, cough, general weakness, headache, myalgia, sore throat, nose discharge/swelling, nausea/vomiting or diarrhoea [5].

Recently, as part of a multicentric study in Emilia Romagna, Northern Italy (June to August 2020) [6], we assessed the diagnostic performances of clinical criteria regarding 90 morbidly obese patients who had undergone a diagnostic test for SARS-CoV-2 infection with RT-qPCR on nasopharyngeal specimens (Table 1). In this group, 21.1% were males with mean age 46.4 ± 10.6 and BMI of $35.3\,kg/m^2 \pm 4.6$. All in all, 14 (15.6%) patients had SARS-CoV-2 infection confirmed by RT-qPCR. All subjects were specifically interviewed about any symptoms included in the WHO case definition about which they had complained since February 2020. Association between SARS-CoV-2 infection and reported symptoms was calculated by means of Chi^2 test with Yates correction. All symptoms that in univariate analysis were associated with a positive RT-qPCR test were included in a binary logistic regression model as explanatory variables. Sensitivity, specificity, predicted positive/negative values, and test agreement (i.e. Cohen's kappa) were calculated by means of 2×2 tables.

Interestingly, 48 out of 90 morbidly obese patients were "*probable cases*" (53.3%) according to the WHO case definition, but only fever ($T > 37.5\,^{\circ}C$ or having a sudden onset), cough, anosmia/ageusia, myalgia, and asthenia were associated with positive RT-qPCR status. As anosmia and ageusia were highly correlated ($r = 0.865$, $P < 0.001$), a dummy variable "anosmia OR ageusia" was included in logistic regression analysis. Finally, only cases reporting either anosmia or ageusia (aOR 51.002 95%CI 3.359 to 774.441) were significantly associated with the positive RT-qPCR assay outcome variable.

Clinical case definition exhibited exceedingly high sensitivity (100%), but low specificity (55.3%) and minimal agreement (0.278) with laboratory diagnostics (see Table 2). While reporting of either anosmia or ageusia was characterized by exceedingly high sensitivity (92.9%), and moderate specificity (73.7%) with weak agreement (0.428), myalgia and asthenia were characterized by moderate sensitivity (71.4% in both cases) and specificity (79.0% for myalgia, 73.7% for asthenia), with no agreement (0.373 for myalgia, 0.323 for asthenia). Assuming as probable that all cases presenting at least one symptom among fever, cough, anosmia, ageusia, myalgia, asthenia were reported, sensitivity of 100% was found, along with specificity of 60.5% and minimal agreement (0.323).

Despite the limits of our study, particularly convenience sampling without preventive power analysis, self-reporting of symptoms, and the reduced number of participants with a potential oversampling of SARS-CoV-2 positive cases, our estimates confirm that the clinical case definition of "probable" COVID-19 cases may potentially be useful, but is not totally reliable in morbidly obese patients. Although exceedingly high sensitivity substantially rules out the risk of misdiagnosing actual COVID-19 cases, with subsequent delays in treatment and confinement procedures, unsatisfactory specificity means that a high proportion of assessed patients will be at risk of receiving unnecessary and costly treatment, with a possible waste of valuable resources. On the other hand, our estimates suggest that, when dealing with morbidly obese patients in a setting with high SARS-CoV-2 endemicity, as was Emilia Romagna Region at the time of our survey [6], reporting at least one among a group of six symptoms (i.e. fever $> 37.5\,^{\circ}C$, cough, anosmia, ageusia, myalgia, asthenia) should suffice to raise clinical suspicion. This is particularly true for patients with anosmia or ageusia, while the clinician should be cognizant of the fact that symptoms such as productive sore throat, running nose, productive cough, shivering, nausea, diarrhea, headache and conjunctivitis are apparently of lesser reliability in obese patients [5,6]. However, as neither the WHO case definition nor a revised assessment of clinical symptoms radically improved diagnostic performances *per se*,

Table 1
Characteristics of 90 morbidly obese patients included in the study, and associations of symptom complaints with a positive diagnosis of SARS-CoV-2 (RT-qPCR). Univariate analysis was performed by means of Chi^2 test. All variables that in univariate analysis were associated with a positive RT-qPCR assay (i.e. outcome variable) having a *P* value < 0.05 were included as explanatory variables in a binary logistic regression model calculating correspondent adjusted Odds Ratio (aOR) with their 95% confidence intervals (95%CI).

	Total No./90, %	RT-qPCR pos. No./14, %	RT-qPCR neg. No./76, %	Chi^2 test *P* value	aOR (95%CI)
Age (years)				0.196	-
< 30	7, 7.8%	1, 7.1%	6, 7.9%		
30–39	14, 15.6%	0, -	14, 18.4%		
40–49	32, 35.6%	4, 28.6%	28, 36.8%		
50–59	32, 35.6%	8, 57.1%	24, 31.6%		
60–69	3, 3.3%	1, 7.1%	3, 3.9%		
≥ 70	2, 2.2%	1, 7.1%	1, 1.3%		
Male gender	19, 21.1%	4, 28.6%	15, 19.7%	0.698	-
Symptoms					
Fever > 37.5 °C	35, 38.9%	11, 78.6%	24, 31.6%	0.003	2.471 (0.299; 20.421)
Sore throat	14, 15.6%	3, 21.4%	11, 14.5%	0.796	-
Running nose	20, 22.2%	5, 35.7%	15, 19.7%	0.331	-
Cough	19, 21.1%	7, 50.0%	12, 15.8%	0.012	1.440 (0.314; 6.595)
Productive cough	5, 5.6%	0, -	5, 6.6%	0.724	-
Shivering	23, 25.6%	7, 50.0%	16, 21.1%	0.051	-
Anosmia[a]	15, 16.7%	6, 42.9%	9, 11.8%	0.013	N/A
Ageusia[a]	19. 21.1%	8, 57.1%	11, 14.5%	0.001	N/A
Anosmia/Ageusia[a]	33, 36.7%	13, 92.9%	20, 26.3%	< 0.001	51.002 (3.359; 774.441)
Myalgia	26, 28.9%	10, 71.4%	16, 21.1%	< 0.001	0.826 (0.131; 5.593)
Nausea	15, 16.7%	2, 14.3%	13, 17.1%	1.000	-
Diarrhea	19, 21.1%	4, 28.6%	15, 19.7%	0.698	-
Asthenia	30, 33.3%	10, 71.4%	20, 26.3%	0.003	0.306 (0.031; 3.042)
Headache	19, 21.1%	6, 42.9%	13, 17.1%	0.070	-
Conjunctivitis	7, 7.8%	1, 7.1%	6, 7.9%	1.000	-
WHO case definition[b] [6]	48, 53.3%	14, 100%	33, 44.7%	< 0.001	N/A

[a] In order to avoid redundancy because of the high correlation between anosmia and ageusia, a dummy variable represented by anosmia OR ageusia was finally included in the logistic regression mode.

[b] A patient who had experienced since February 24, 2020 at least one episode of anosmia/dysgeusia or had chest imaging suggestive of COVID-19, or an association of rapid onset fever (self-measured temperature ≥ 37.5 °C) and cough, or an association of any three or more of the following signs and symptoms: fever, cough, general weakness, headache, myalgia, sore throat, nose discharge/swelling, nausea/vomiting or diarrhea.

Table 2
Diagnostic performances of the clinical definition of COVID-19, as suggested by the WHO [6], and as refined by inclusion of symptoms that were associated with RT-qPCR-confirmed SARS-CoV-2 infection at univariate analysis (*P* < 0.05, Table 1 Cohen's Kappa values should be interpreted as follows: 0.0–0.20 no agreement, 0.21–0.39 minimal agreement, 0.40–0.59 weak agreement, 0.60–0.79 moderate agreement, 0.80–0.90 strong agreement, > 0.90 almost perfect agreement.

	True Positive	False Positive	False Negative	True Negative	Sensitivity	Specificity	Predicted Positive Value	Predicted Negative Value	Cohen's Kappa
WHO case definition[a] [6]	14, 15.6%	34, 37.8%	0, -	42, 46.7%	100%	55.3%	29.2%	100%	0.278
Fever	11, 12.2%	3, 3.3%	24, 26.7%	52, 57.8%	31.4%	94.6%	78.6%	68.4%	0.292
Cough	7, 7.8%	12, 13.3%	7, 7.8%	64, 71.1%	50.0%	84.2%	36.8%	90.1%	0.299
Anosmia	6, 6.7%	9, 10.0%	8, 8.9%	67, 74.4%	42.9%	88.2%	40.0%	89.3%	0.301
Ageusia	8, 8.9%	11, 12.2%	6, 6.7%	65, 72.2%	57.1%	85.5%	42.1%	91.6%	0.372
Myalgia	10, 11.1%	16, 17.8%	4, 4.4%	60, 66.7%	71.4%	79.0%	38.5%	93.8%	0.373
Asthenia	10, 11.1%	20, 22.2%	4, 4.4%	56, 62.2%	71.4%	73.7%	33.3%	93.3%	0.308
Any of previous symptoms	14, 15.6%	30, 33.3%	0, -	46, 51.1%	100%	60.5%	31.8%	100%	0.323
Anosmia or Ageusia	13, 14.4%	20, 22.2%	1, 1.1%	56, 62.2%	92.9%	73.7%	39.3%	98.3%	0.428

[a] A patient who had experienced since February 24, 2020 at least one episode of anosmia/dysgeusia or had chest imaging suggestive of COVID-19, or an association of rapid onset fever (self-measured temperature ≥ 37.5 °C) and cough, or an association of any three or more of the following signs and symptoms: fever, cough, general weakness, headache, myalgia, sore throat, nose discharge/swelling, nausea/vomiting or diarrhea.

confirmatory diagnosis by means of RT-qPCR on nasal swabs still remains unavoidable [7,8].

Disclosure of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article. The facts, conclusions, and opinions stated in the article represent the authors' research, conclusions, and opinions, and are believed to be substantiated, accurate, valid, and reliable. However, as this article includes the results of personal research of the authors, presenting correspondent, personal conclusions, and opinions, parent employers are not forced in any way to endorse or share its content and its potential implications.

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West Nile Virus infection: Before involving occupational physicians in active surveillance, make sure they are more aware

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In 2008, the mosquito-borne West Nile Virus (WNV) emerged as a human pathogen, when the first human cases of neuroinvasive disease were identified in the Italian Po river Valley [1]. Over the following years, WNV was characterized as an endemic pathogen, and its transmission apparently peaked in 2018, with a total of 610 cases representing 39% of EU cases [2]. As infected humans are generally asymptomatic, and because of the widespread dissemination of the mosquito vector (i.e., *Culex spp*), it is likely that the true prevalence rate of WNV may have been largely underestimated [3–5].

WNV infection represents a potential threat for all outdoor workers, particularly those in the agricultural, forestry and building sectors [3,4]. Epidemiological studies on farmers, agricultural workers and veterinarians have reported serologic IgG positivity ranging from 0.9% to 20.9% [1,5]. However, available evidence is limited to occupational contagions occurring among entomologists, veterinary students, and laboratory workers [3,5], and only sporadic reports have suggested the possible occurrence of WNV infections among outdoor workers in Italy (i.e. increasing occurrence of flu-like syndromes outside the flu season) [4]. Some authors have therefore suggested that more active surveillance by Occupational Physicians (OP) may improve our understanding of WNV epidemiology [3,4]. Moreover, as OPs are the medical professionals responsible for workplace health promotion, by tailoring appropriate preventive recommendations to specific occupational settings they could possibly reduce the global burden of the disease, at least in high-risk areas [3–5]. Unfortunately, to date OPs have been seldom been questioned about their knowledge (i.e., awareness of official recommendations), attitudes (i.e., propensity towards a certain intervention), and practices (i.e., collective promotion of such intervention) regarding arbovirus infections, including WNV [6].

Wishing to fill the attendant information gap, we conducted a cross-sectional questionnaire-based study (01/02/2020-28/02/2020) on OPs participating in seven professional group pages and four closed forums (2034 single members). Estimates on Tick-Borne Encephalitis had previously been reported [6]. In this paper, we report a follow-up inquiry focusing on WNV that included a total of 174 OPs from high-risk Italian regions (i.e. Emilia-Romagna, Lombardy, Veneto, Friuli Venezia Giulia, Sardinia, Puglia). Characteristics of the participants are summarized in Table 1. Briefly, 67.9% of them were ≥ 40-years-old, and 54.0% were male. Two thirds reported knowledge of the term "arbovirus", while only 8.6% had any professional interaction with cases of WNV infection. Knowledge status of participants was assessed through a test that included a series of 21 true/false statements on WNV infection. A summary knowledge score (KS) was then calculated by adding +1 for every correct answer. After percent normalization, a cumulative KS of 64.6% ± 14.0 (median 64.3%) was calculated. Interestingly, only one third of participants had any awareness of the occurrence of human WNV cases in the Italian region where they lived and/or worked, while diffuse misunderstandings about the ecology of WNV, as well as other arboviruses, were identified. For instance, around 1/3 of respondents were unaware that WNV has no inter-human spreading. Regarding the participants' risk perception, in a scale ranging from "of no significant concern in daily practice" (score = 1) to "of very high concern in daily practice" (score = 5), WNV incidence was acknowledged as concerning/highly concerning (i.e. a frequently reported disease) by 30.5% of respondents, while only 8.6% reported concerns on its severity. High-risk status for agricultural workers was acknowledged by 85.1% of respondents, followed by forestry workers (69.5%), while only 21.3% of participants exhibited similar concerns for construction workers. Regarding the recommended preventive measures, 74.6% of participants favored the removal of standing waters from occupational settings, while their treatment with insecticide/larvicide was reported by 64.4%. Highly effective use of skin repellents was recommended by 69.5% of participants, whereas only a third of them recommended the diffuse disposal of pesticides and the wearing of light-colored clothing (37.5%, and 30.5%, respectively). All in all, 69.0% of respondents recommended three or more of the aforementioned preventive measures [7,8]. Assuming the promotion of three or more preventive measures as outcome variable (Table 2), its association with other individual factors was assessed through calculation of adjusted Odds Ratios (aOR) with their 95% confidence intervals (95%CI) by means of a binary logistic regression model. While belonging to older age groups was characterized as a negative behavioral predictor (i.e. aOR 0.217, 95%CI 0.076 to 0.624), acknowledging a higher risk status for WNV infection in agricul-