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Letter to the Editor

Trend in the proportion of subjects with SARS-CoV-2 infection without COVID-19 specific symptoms among patients admitted to a COVID-19 referral hospital

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Dear editor

The clinical and epidemiological characteristics of COVID-19 gradually changed during different waves [1]. The highly transmissible omicron variant that has globally dominated during 2022 has led to an unprecedented surge in the number of infections although producing lower hospital admission rates and less severe disease amongst the patients who are admitted [2]. Moreover, a recent study in the United States has estimated that almost 14% of the SARS-CoV-2 positive patients admitted to hospitals during the omicron BA1 wave had a reason for admission other than COVID-19 (cases of incidental COVID-19) [3], and study conducted in The Netherlands during the omicron BA.1/BA.2 wave found that 31% of the patients admitted with COVID-19 could be classified as incidental COVID-19 cases [4]. Continuing to monitor the clinical characteristics of hospitalised subjects with SARS-CoV-2 infection is therefore a crucial means of ensuring an appropriate response to the evolving picture of the disease.

The aim of this study was to compare the characteristics of the patients hospitalised at a COVID-19 referral centre in Milan, Italy, during the last three consecutive waves of the COVID-19 epidemic.

This was a repeated cross-sectional study carried out at the Department of Infectious Diseases and Intensive Care Unit of Luigi Sacco hospital, which has acted as a COVID-19 referral centre for the city of Milan since the start of the epidemic in Italy. We extracted from our prospective COVID-19 hospital registry (the characteristics of which have been extensively described elsewhere [1,5-7]) the patients who were hospitalised on a random day of the week of peak COVID-19 hospitalisations during the third, fourth and fifth waves (W3-W5) of the Italian epidemic: the third week of March 2021, the third week of January 2022, and the fourth week of July 2022. National surveillance data indicate that W3 was a pre-delta wave characterised by the predominance of the alpha variant, W4 was characterised by the first omicron surge in Italy, and W5 was characterised by a mix of omicron sub-variants (0.4% BA1.1, 29.7% BA.2, 13% BA.4, and 56.7% BA.5) [8].

The demographic and clinical characteristics of the selected patients were used to categorise them on the basis of the current COVID-19 treatment guidelines as cases of mild, moderate, severe or critical COVID-19, or cases of SARS-CoV-2 infection (confirmed by a positive nasopharyngeal swab test) without any COVID-19-specific symptoms. The reasons for the hospitalisation of the asymptomatic patients were also examined. The descriptive statistics use proportions for categorical variables, and median values and IQRs for continuous variables. The demographic and clinico-epidemiological characteristics of the patients by period of hospital stay were compared using the χ^2 test or, when necessary, Fisher's exact test in the case of categorical variables or Wilcoxon's rank-sum test in the case of continuous variables.

On the randomly selected days during W3, W4 and W5, there were respectively 153, 119 and 62 hospitalised patients with SARS-CoV-2 infection: Table 1 shows their demographic and clinical characteristics. The median age of the patients progressively increased from 68 (IQR 57–76) years in W3, to 75 (IQR 65–84) years in W4, and 84 (IQR 79–90) years in W5 ($p<0.001$). The median time from symptom onset to admission progressively decreased from nine (IQR 7–10) days in W3 to seven (IQR 4–10) days in W4 and 3 (IQR 2–5) days in W5 ($p<0.001$). The only patient to have received early SARS-CoV-2 treatment before hospitalisation was one hospitalised during W5. The severity of the disease significantly decreased, with 53 (34.6%) of the patients hospitalised during W3 having critical disease as against 14 (11.8%) hospitalised during W4 and two (3.2%) hospitalised during W5 ($p<0.001$). The proportion of patients hospitalised with SARS-CoV-2 infection but without COVID-19-specific symptoms significantly increased from 0.7% in W3 to 18.5% in W4 and 40.3% in W5 ($p<0.001$). The main reasons for hospitalisation of subjects without COVID-19 specific symptoms during W4 and W5 were similar: surgical procedures (5/22 and 4/25), acute cardiovascular disease (2/22 and 4/25), acute neurological disorders (3/2 and 2/25), psychiatric disorders (3/22 and 0/25), and complicated urinary tract infections (3/22 and 3/25).

Our data show a trend towards a reduction of the number of patients hospitalised at our COVID-19 referral centre with SARS-CoV-2 infection and COVID-19-specific symptoms during the current wave of infections due to the omicron variant that is line with national estimates [9]. The proportion of asymptomatic SARS-CoV-2 infections reached 40% during the latest peak of COVID-19 hospitalisations at the end of July 2022, when infections due to the omicron sub-variants BA.2, BA.4 and BA.5

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Table 1
Characteristics of the study population.

	W3 $n = 153$	W4 $n = 119$	W5 $n = 62$	p-value
Biological sex, n (%)				
Female	52 (34.0)	59 (49.6)	29 (46.8)	*0.024*
Male	101 (66.0)	60 (50.4)	33 (53.2)	
Median age, years (IQR)	68 [57, 76]	75 [65, 84]	84 [79, 90]	*<0.001*
Age strata, n (%)				
<46	11 (7.2)	7 (5.9)	1 (1.6)	*<0.001*
46–60	36 (23.5)	17 (14.3)	1 (1.6)	
61–75	69 (45.1)	40 (33.6)	9 (14.5)	
>75	37 (24.2)	55 (46.2)	51 (82.3)	
Median CCI, median [IQR]	3 [2, 5]	4 [3, 6]	5 [5, 7]	*<0.001*
Co-morbidities				
Obesity, n (%)	46 (30.1)	37 (31.1)	6 (9.7)	*0.004*
Diabetes, n (%)	32 (20.9)	18 (15.1)	6 (9.7)	0.114
Lung disease, n (%)	18 (11.8)	28 (23.5)	17 (27.4)	*0.008*
Heart disease, n (%)	97 (63.4)	70 (58.8)	53 (85.5)	*0.001*
Renal disease, n (%)	10 (6.5)	19 (16.0)	11 (17.7)	*0.018*
Oncological disease, n (%)	13 (8.5)	25 (21.0)	14 (22.6)	*0.004*
Immune system disorder, n (%)	9 (5.9)	10 (8.4)	5 (8.1)	0.696
Liver disease, n (%)	7 (4.6)	5 (4.2)	0 (0)	0.239
X-ray documenting pneumonia upon admission, n (%)	149 (97.4)	85 (71.4)	25 (40.3)	*<0.001*
Median number of days from admission to data collection (IQR)	9 [5, 14]	8.00 [3, 16]	7[2, 14]	0.245
O_2 therapy support at the time of data collection, n (%)				
No O_2	43 (28.1)	60 (50.4)	29 (46.8)	*<0.001*
Nasal cannula	26 (17.0)	22 (18.5)	18 (29.0)	
Venturi	27 (17.6)	20 (16.8)	10 (16.1)	
Reservoir	4 (2.6)	3 (2.5)	2 (3.2)	
C-PAP	26 (17.0)	7 (5.9)	3 (4.8)	
MV	27 (17.6)	7 (5.9)	0 (0)	
Disease severity at the time of data collection, n (%)				
No COVID-19-related symptoms	1 (0.7)	22 (18.5)	25 (40.3)	*<0.001*
Mild	2 (1.3)	8 (6.7)	10 (16.1)	
Moderate	66 (43.1)	52 (43.7)	15 (24.2)	
Severe	31 (20.3)	23 (19.3)	10 (16.1)	
Critical	53 (34.6)	14 (11.8)	2 (3.2)	
SARS-CoV-2 vaccine, n (%)	1 (0.7)	72 (60.5)	58 (93.5)	*<0.001*
Doses of SARS-CoV-2 vaccine, n (%)				
0	152 (99.3)	47 (39.5)	4 (6.7)	*<0.001*
1	1 (0.7)	6 (5.0)	1 (1.7)	
2	0 (0)	45 (37.8)	6 (10.0)	
3	0 (0)	21 (17.6)	49 (81.7)	

List of abbreviations: n, number; IQR, Inter Quartile Range; CCI, Charlson co-morbidity index; C-PAP, Continuous Positive Airway Pressure; MV, Mechanical Ventilation.

were spreading throughout Italy [8]. This finding is consistent with what was initially observed after the emergence of the omicron variant in the US [3] and other European countries [4]. A number of factors may have contributed to the changes observed by us. First of all, the successful development and roll-out of effective vaccines dramatically reduced the odds of SARS-CoV-2 infected subjects developing severe/critical disease [2], and the availability of early antiviral and monoclonal treatments further reduced the likelihood of hospitalisation amongst subjects at increased risk of severe COVID-19 [10]. Secondly, omicron variant is more transmissible but less virulent than its predecessors [8] and, although it has increased the total number of SARS-CoV-2 infections detected in the general population, this has not been accompanied by a proportional increase in hospitalisations due to COVID-19 [8]. Furthermore, the increased spread of omicron variants in the general population may also explain the increasing number of people who need to be hospitalised for reasons other than COVID who incidentally test positive for SARS-CoV-2. Our observation of a predominance of elderly, fully vaccinated subjects with a high co-morbidity burden during W5 should not be considered surprising because: 1) it is known that the vaccines are most effective in younger subjects,; 2) SARS-CoV-2 infection can worsen the general condition of frailer subjects; and 3) although the time from symptom onset to hospital admission was within the window of opportunity for effective early treatment during W5, only one patient actually received an anti-viral agent before being hospitalised.

Many Italian hospitals still continue the existence of COVID-19-dedicated wards that were originally intended to provide adequate isolation and respiratory support to COVID-19 patients with respiratory symptoms. This policy may now be questionable and consideration should be given to creation of isolation areas ('bubbles') in every specialist ward in order to provide optimal care to SARS-CoV-2 positive patients requiring hospitalisation for reasons other than COVID-19.

The main limitations of our study are the use of a convenience sample of subjects in order to provide a picture of hospitalised subjects during the peak periods of different epidemic waves and that our observations are limited to setting in which dedicated COVID-19 wards admit patients solely on the basis of a positive naspharyngeal swab.

In conclusion, the characteristics of hospitalised subjects with SARS-CoV-2 infection evolved during the course of the pandemic, and 40% of those admitted to our COVID-19 referral centre during the last epidemic period were admitted for reasons other than COVID-19. The persistent predominance of elderly patients and patients with multiple morbidities amongst COVID-19 cases suggests the need to strengthen preventive interventions that counteract the current under-use of early antiviral and monoclonal treatments in outpatients and encourage the uptake of booster doses of COVID-19 vaccines.

Authors' contributions

AG and ALR designed the study; AG and LO were responsible for the statistical analysis. All of the authors contributed to patient enrolment, and the collection and interpretation of the data. GR, ALR and SA supervised the project. AG prepared a preliminary draft of the manuscript, which was critically reviewed by ALR and SA. All of the authors have read and approved the final manuscript.

Data availability statement

The complete dataset will be provided in txt format upon reasonable request to the corresponding author.

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Declaration of Competing Interest

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Ethics approval statement

This study was approved by our Ethics Committee (Comitato Etico Interaziendale Area 1, Milan, Italy: Protocol No. 16088).

Patient consent statement

Informed consent was obtained directly from the patients capable of making informed decisions about their medical care and participation in the study; otherwise, informed consent was obtained from his/her legal guardian or representative.

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