

Estimating the proportion of asymptomatic COVID-19 cases during the first pandemic wave in Apulia region, Italy

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Abstract

In the current epidemiological situation of COVID-19 in countries such as Italy, quantifying the contribution of asymptomatic infections to SARS-CoV-2 transmission is of crucial importance for pandemic control. We conducted a retrospective epidemiological study to characterize asymptomatic COVID-19 cases occurred in the Apulia region, Italy, during the first epidemic wave of COVID-19 outbreak.

We analyzed data collected in a regional surveillance platform developed to manage the emergency through investigation and follow-up of cases and contacts, contact tracing, laboratory and clinical data collection. We included asymptomatic laboratory-confirmed cases defined as persons infected with SARS-CoV-2 who did not develop symptoms/clinical signs of the disease.

Between February 29 and July 7, 2020, a total of 4,536 cases were diagnosed with COVID-19 among 193,757 tests performed. The group of persons with asymptomatic SARS-CoV-2 infection consisted of 903 cases; the asymptomatic proportion was 19.9% (95%CI: 18.8-21.1%); this decreased with increasing age (OR: 0.89, 95%CI: 0.83-0.96; $p=0.001$), in individuals with underlying comorbidities (OR: 0.55, 95%CI: 0.41-0.73; $p<0.001$), and males (OR: 0.69, 95%CI: 0.54-0.87; $p=0.002$). The median asymptomatic infectious period was 19 days (IQR: 14-31) and the cumulative proportion of persons with resolution of infection 14 days after the first positive PCR test was 74%.

In Europe and globally, there is again an increase in the number of new cases, mainly asymptomatic. As the public health community debates the question of whether asymptomatic and late spreaders could sustain virus transmission in the communities, such cases present unique opportunities to gain insight into SARS-CoV-2 adaptation to human host.

Key words

Asymptomatic; COVID-19; SARS-CoV-2; Infection; Italy

Introduction

Since coronavirus disease 2019 (COVID-19) burst onto the global scene, asymptomatic transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has appeared as the “Achilles’ heel” of Covid-19 pandemic control through the traditional public health interventions [1]. Understanding the possible role of transmission by asymptomatic individuals is crucial to improve surveillance and containment measures and attempt to estimate the likely burden of severe disease and mortality when the virus spreads in the communities [2]. However, information on the natural history of infection with SARS-CoV-2 is currently not enough for quantifying the contribution of persons with asymptomatic COVID-19 infection to COVID-19 transmission [3].

On July 7, 2020, a total of 11,500,302 COVID-19 cases were diagnosed in the world. Exactly 137 days since the first confirmed COVID-19 case was announced, Italy was the eleventh most affected country, with 241,819 total cases and 34,869 deaths [4]. Worldwide, the proportion of asymptomatic infection was estimated to be 10.1-23.0% of all confirmed cases [5].

Here, we conducted a retrospective epidemiological study to quantify and characterize asymptomatic COVID-19 cases occurred in the Apulia region of the southern part of Italy from February 29 to July 7, 2020.

Results

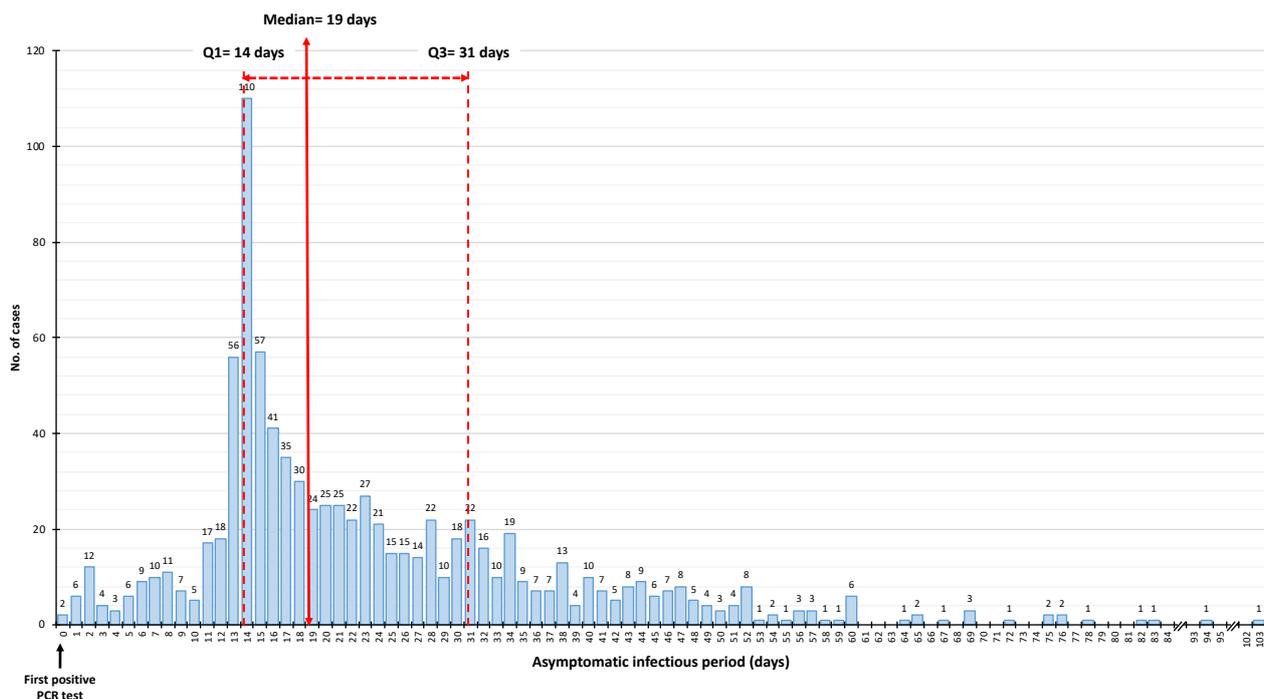
Between February 29 and July 7, 2020, a total of 4,536 cases (51.1% male; median age: 56 years, IQR: 41-72) were diagnosed with COVID-19 in the Apulia region, Italy.

The group of persons with asymptomatic SARS-CoV-2 infection consisted of 903 (53.5% female) cases among 193,757 tests performed, with median age of 50 years (IQR: 32-63). A total of 146

(16.5%) of these patients had underlying medical conditions, including cardiovascular disease (9.2%), diabetes (1.6%) and chronic lung disease (1.2%) (Information on underlying diseases was only available for 335 cases).

The asymptomatic proportion was estimated to be 19.9% (95% confidence interval (CI): 18.8-21.1%). The median asymptomatic infectious period was 19 days (IQR: 14-31) and the cumulative proportion of persons with resolution of infection 14 days after the first positive PCR test was 74% (Figure).

Figure. Asymptomatic infectious period of persons with confirmed COVID-19, Apulia region, Italy, February-July 2020



The probability of having asymptomatic infection decreased with increasing age (Odd Ratio for being asymptomatic with each 10-year increase in age: 0.89, 95% CI: 0.83-0.96, $p=0.001$), in individuals with underlying diseases (OR: 0.55, 95% CI: 0.41-0.73, $p<0.001$), and in males (OR: 0.69, 95% CI: 0.54-0.87, $p=0.002$). The risk of delayed resolution of infection increased with increasing age, with

median asymptomatic infectious period increasing from 16.5 days (IQR:14-26) in persons aged 0-9 years to 28 days (IQR: 18-40) in those aged 80-89 years ($p < 0.001$).

Discussion

After the end of the first epidemic wave of COVID-19 outbreak in Italy, we tried to estimate the proportion of people with SARS-CoV-2 who were asymptomatic in the Apulia region. Our findings show that between 18.8% and 21.1% of people testing positive for SARS-CoV-2 were asymptomatic. These estimates are consistent with the pooled percentage of asymptomatic infection (15.6%, 95% CI: 10.1%-23.0%) estimated by a recent meta-analysis [5]. However, in the Lavezzo et al. prospective cohort study conducted in the Italian municipality of Vò it was reported that the 42.5% of confirmed SARS-CoV-2 infections were asymptomatic [8]. This difference could be explained by the fact that in our study we analyzed a larger number of cases. Moreover, the retrospective nature of the study itself allowed us to exclude from the analysis the asymptomatic individuals who developed symptoms later during follow-up. In fact, presymptomatic patients are easily misclassified as asymptomatic if the follow-up is not long enough and this may lead to overestimate the true burden of asymptomatic infection [5].

From the beginning of the pandemic of SARS-CoV-2, age, prior illnesses and sex have emerged as risk factors [5]. Our results show that asymptomatic infections were more common in young individuals without underlying diseases and among females. This is usually seen during other respiratory virus infections such as the influenza virus.

Following the third phase of activity reopening on June 3, the Italian monitoring system has been enriched with new data including information on the reason why the individual is tested (i.g. diagnostic suspicion that emerge during clinical activities, screening/tracing activities that emerge

via planned tests of travellers returning to Italy from foreign countries with higher virus circulation, immigrants, and employees). As a result, between July 8 and August 18, 2020, it was reported that overall 76% of asymptomatic cases seen in the Apulia region were aged between 0 and 50 years (median age: 28 years) (unpublished observations). It is likely that the difference between the medians of age of asymptomatic cases in the two consecutive periods reflected the sensitivity of case finding and diagnostic protocols rather than the true disease epidemiology.

Our data show that one in four asymptotically infected person had a positive nucleic test result to more than four weeks after the first test (Figure), this may indicate that the long-term infection of SARS-CoV-2 might really do exist. In particular, among asymptomatic cases, long-term carrying of the virus was more common for older persons than the youngest cases.

This study has two main limitations. First, asymptomatic cases in our cohort were mostly close contacts of cases with symptoms detected during the contact tracing activities. Therefore, they may have represented a peculiar fraction of the SARS-CoV-2 asymptomatic transmission. Moreover, for the same reason, it is very likely that asymptomatic proportion of cases has been underestimated. Second, the peak of resolution of infection observed at 14 days (Figure) is an artefact of the surveillance and depends on the fact that many cases are tested at day 14 before exiting the quarantine period. Anyhow, such peak does not affect either median or Q3 value calculation that are very likely to be 19 and 31 days respectively.

Identifying asymptomatic cases is of crucial importance for SARS-Cov-2 in the current transitional epidemiological phase. Indeed, in Italy, as in other European countries and globally, there is again an increase in the number of new cases diagnosed and reported, and this increase is mainly in asymptomatic cases [9], also as a result of strengthening of diagnostic activities that allow to implement screening test strategies in high-risk groups of population. The presence of a large

proportion of asymptomatic (and late) spreaders of the virus is a challenge for controlling the pandemic. Even though we do not know the level of infectivity of long-term virus carriers, we cannot exclude that they have a residual risk of spreading the infection. According to the recent WHO guidelines, 10 days after the positive test for SARS-CoV-2, even in the absence of a negative test, asymptomatic cases can be released from quarantine [10].

The presence of asymptomatic, late spreaders must be taken into consideration if such subjects can get in contact with fragile population, as in the case of health care personnel and elderly homes workers. Moreover, this may represent the main way SARS-Cov-2 is becoming endemic in humans adapting to the new host.

Methods

We analyzed data collected in a regional surveillance platform (GIAVA - COVID[®]) developed on the basis of the Go.Data outbreak investigation tool (WHO) [6] to manage the emergency. GIAVA - COVID[®] includes functionalities for investigation and follow-up of cases (until having two consecutive negative RT-PCR test results at least 24 hours apart) and contacts (during the 14-day isolation period), contact tracing, demographics, laboratory and clinical data collection.

This study included asymptomatic laboratory-confirmed cases defined as persons infected with SARS-CoV-2 who did not develop symptoms or clinical signs of the disease. The asymptomatic proportion was defined as the proportion of infected individuals who had no clinical signs or symptoms compatible with COVID-19 among the total number of infected individuals [7]. The asymptomatic infectious period was defined as the number of days between the first positive PCR test and the first of the two serial negative PCR tests.

Categorical variables were summarized as the counts and percentages in each category. Continuous variables were expressed as the medians and interquartile ranges (IQR). Kruskal-Wallis test was

applied to continuous variables. Multivariate logistic regression analysis was performed to evaluate whether patients' demographics and clinical characteristics were independently associated with having asymptomatic infection. Analysis was conducted with STATA/SE 15.0.

As this study constituted public health surveillance, ethical approval from institutional review board was not required. All data were provided and analyzed anonymously.

Declarations

Funding

No funding was received for conducting this study.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval

As this study constituted public health surveillance, ethical approval from institutional review board was not required. All data were provided and analyzed anonymously.

Author Contribution Statement

R.P., P.L.L. and D.M. conceived and designed the study. F.F. and D.M. analysed the data and prepared the figure. L.B. contributed to the data collection and managed the database. S.M. contributed to the interpretation of data. R.P. and D.M. drafted the manuscript with substantial contributions from all authors. All authors approved the submitted version of the manuscript.

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Availability of materials and data

The data that support the findings of this study are available from the Apulia Public Health Authority but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Apulia Public Health Authority.

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