Early predictors of clinical deterioration in a cohort of outpatients with COVID-19 in southern Italy: A multicenter observational study

Caterina Monari1 | Mariantonieta Pisaturo1 | Paolo Maggi2 | Margherita Macera2 | Giovanni Di Caprio2 | Raffaella Pisapia3 | Valeria Gentile1 | Mario Fordellone4 | Paolo Chiodini4 | Nicola Coppola1 | CoviCam Group

1Department of Mental Health and Public Medicine, Infectious Diseases Unit, University of Campania Luigi Vanvitelli, Naples, Italy
2Infectious Disease Unit, AORN Caserta, Caserta, Italy
3Infectious Diseases Unit, AORN dei Colli, Naples, Italy
4Medical Statistics Unit, University of Campania Luigi Vanvitelli, Naples, Italy

Correspondence
Nicola Coppola, Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania Luigi Vanvitelli, Naples, Via L. Armanni 5, 80131 Naples, Italy.
Email: nicola.coppola@unicampania.it

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Abstract
Data regarding early predictors of clinical deterioration in patients with infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still scarce. The aim of the study is to identify early symptoms or signs that may be associated with severe coronavirus disease 2019 (COVID-19). We conducted a multicentre prospective cohort study on a cohort of patients with COVID-19 in home isolation from March 2020 to April 2021. We assessed longitudinal clinical data (fever, dyspnea, need for hospitalization) through video calls at three specific time points: the beginning of symptoms or the day of the first positivity of the nasopharyngeal swab for SARS-CoV-2 RNA (t0), and 3 (t3) and 7 (t7) days after the onset of symptoms. We included 329 patients with COVID-19: 182 (55.3%) males, mean age 53.4 ± 17.4 years, median Charlson comorbidity index (CCI) of 1 (0–3). Of the 329 patients enrolled, 171 (51.98%) had a mild, 81 (24.6%) a moderate, and 77 (23.4%) a severe illness; 151 (45.9%) were hospitalized. Compared to patients with mild COVID-19, moderate and severe patients were older (p < 0.001) and had more comorbidities, especially hypertension (p < 0.001) and cardiovascular diseases (p = 0.01). At t3 and t7, we found a significant higher rate of persisting fever (≥37°C) among patients with moderate (91.4% and 58.0% at t3 and t7, respectively; p < 0.001) and severe outcome (75.3% and 63.6%, respectively; p < 0.001) compared to mild COVID-19 outcome (27.5% and 11.7%, respectively; p < 0.001). Factors independently associated with a more severe outcome were persisting fever at t3 and t7, increasing age, and CCI above 2 points. Persisting fever at t3 and t7 seems to be related to a more severe COVID-19. This data may be useful to assess hospitalization criteria and optimize the use of resources in the outpatient setting.

KEYWORDS
COVID-19, early predictors, fever, SARS-CoV-2 infection, severe outcome
1 | INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) started in Wuhan, China, in December 2019 and has rapidly spread to a pandemic proportion worldwide.\(^3\) By February 14th, 2022, over 410 million confirmed cases of COVID-19 and over 5.8 million related deaths had been reported to the World Health Organization (WHO).\(^5\) After 2 years of the pandemic, it continues to strain healthcare systems all around the world.

Since the beginning of the pandemic, many progresses have been achieved in the knowledge of SARS-CoV-2 and of COVID-19 pathogenesis, as well as in diagnostic, clinical, preventive, and therapeutic fields.\(^3\)\(^4\) A wide range of clinical manifestations and outcomes of COVID-19 have been reported, from asymptomatic to mild respiratory infections, pneumonia, acute respiratory distress syndrome (ARDS), and life-threatening multiple organ failure. Severe clinical presentation of COVID-19 has been associated with age above 55 years, male sex, presence of comorbidities, extensive lung involvement, hypoxemia, and some laboratory test abnormalities, such as low lymphocyte count or increased white blood cell count, blood creatinine, aspartate aminotransferase, lactate dehydrogenase (LDH), interleukin-6, ferritin, α-dimer, and C-reactive protein (CRP).\(^5\)\(^7\) However, also patients initially presenting with mild symptoms can develop severe disease, and would benefit from early and aggressive intervention.\(^8\) So far, precise clinical determinants suggestive of a higher risk of developing severe COVID-19 are still lacking.

The identification of clinical factors potentially associated with severe COVID-19 is of paramount importance and may help healthcare professionals to personalize treatment, especially in the current era of early efficacious treatment, i.e., antivirals and monoclonal antibodies, according to the risk factors of each subject and to allocate proper resources at all levels of care.

Considering these unmet needs, the aim of the present study is to identify early clinical symptoms or signs that could predict a more severe clinical outcome of COVID-19 in a cohort of initially not-hospitalized COVID-19 patients.

2 | METHODS

2.1 | Study design and setting

We performed a multicentre prospective cohort study, according to the STROBE guidelines for the cohort study,\(^7\) involving three COVID-19 units in two cities in the Campania region in southern Italy, Naples and Caserta. The study population included all adult patients (≥18 years) with a diagnosis of SARS-CoV-2 infection, referred to one of the three centers participating in the study on the first day of the onset of symptoms or of SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) nasal oropharyngeal swab-positivity, from March 2020 to April 2021. All the enrolled patients received care at home and were evaluated by video calls in the first days of infection. The clinical longitudinal evaluations in the first days were associated with the subsequent outcome of infection on Day 28 after the onset of symptoms. Thus, to better define the early clinical outcome, we assigned the severity group to patients after we had collected all the clinical information. Exclusion criteria included minority age, lack of clinical data, and/or informed consent. No study protocol or guidelines regarding the criteria of hospitalization were shared among the centers involved in this study and the patients were hospitalized according to the decision of the physicians of each center.

2.2 | Data collection

All demographic and clinical data of patients with SARS-CoV2 infection enrolled in the study were collected in an electronic database. Precisely, a prescheduled questionnaire collecting demographic data, medical history, and the presence or absence of signs (fever and cough) and symptoms (dyspnea, hypoxemia, and hypoaguesia), and exploring the progression of symptoms, was filled out by healthcare professionals through video calls at the onset of symptoms or the first day of SARS-CoV-2 RT-PCR naso-oropharyngeal swab-positivity (t\(_0\)), at Day 3 (t\(_3\)) and Day 7 (t\(_7\)).

2.3 | Variables and definitions

Microbiological diagnosis of SARS-CoV-2 infection was defined as a positive RT-PCR test on a naso-oropharyngeal swab.

We divided patients into three groups, i.e., mild, moderate, and severe, according to the WHO definitions. Precisely, patients with a mild infection remained asymptomatic or experienced a mild infection without evidence of viral pneumonia or hypoxia.\(^10\)\(^11\) Patients with a moderate illness experienced clinical signs of lower respiratory disease and required low flow oxygen (O\(_2\)) therapy.\(^10\)\(^11\) Lastly, patients with severe COVID-19 had severe or critical disease, i.e., patients in ARDS, management in an intensive care unit (ICU) and/or mechanical ventilation, and/or death.\(^11\)

The presence of underlying chronic diseases was defined according to the age-adjusted Charlson comorbidity index (CCI).

2.4 | Statistical analysis

Continuous variables were reported either as mean and standard deviation (SD) or as the median and interquartile range (IQR). Categorical variables were reported as absolute numbers and percentages. We performed a comparison of patients with mild, moderate, and severe COVID-19 using one-way analysis of variance or Kruskal–Wallis test (according to their distribution assessed by the Shapiro–Wilk test), and Pearson χ\(^2\) test for continuous and categorical variables, respectively.\(^12\)\(^15\)

To assess the degree of severity of COVID-19 a proportional odds linear regression (POLR) model with a three levels (i.e., mild,
moderate, and severe) endpoint was used. The POLR model is a class of generalized linear models used for modeling the dependence of an ordinal response on discrete or continuous covariates. In particular, three different POLR models were performed using as covariates fever at 0, 3, and 7 days from the COVID-19 diagnosis, respectively. Moreover, these models were adjusted by age, sex, and CCI. Fever was considered as a three-levels ordinal variable, age as a discrete variable, sex as a binary categorical variable, and CCI as a three-level ordinal variable. Akaike information criterion (AIC), Bayesian information criterion (BIC), and the pseudo-$R^2$ proposed by McFadden were used for evaluating models.

3 RESULTS

In the study period, we included 329 patients. Table 1 describes the main characteristics of subjects, also according to the outcome of the illness: 55.3% of subjects were males, mean age was 53.4 years ± 17.4 SD, median CCI was 1.0 points (IQR: 0, 3.0), and the main reported comorbidity was arterial hypertension (42.2%). Out of the total subjects, 151 (45.9%) needed hospitalization, and 27 died (8.2%).

Among the 329 subjects enrolled, 171 (51.98%) experienced mild, 81 (24.6%) moderate, and 77 (23.4%) severe outcomes (Table 1). Patients with moderate or severe COVID-19 were older (56.6 years ± 15.6 SD and 66.2 years ± 14.9 SD, respectively, vs. 46.2 years ± 15.6 SD, p < 0.001) and needed more frequently hospitalization (84% and 61%, respectively, vs. 21.1% in mild infections, p < 0.001). Patients with severe COVID-19 were characterized by a higher median of CCI, in particular, a higher rate of hypertension (p < 0.001) and cardiovascular diseases (p < 0.001). Moreover, they showed a higher mortality rate compared to moderate and mild illness presentation (33.8% vs. 1.2% in moderate and 0% in mild disease, p < 0.001).

Tables 2–4 describe the main symptoms at the three time points (t0, t3, and t7) according to the severity of the clinical outcome of COVID-19.

At the onset of symptoms or the first SARS-CoV-2 RT-PCR naso-oropharyngeal swab-positivity (t0), the majority of patients (51.1%) experienced fever with temperatures between 37°C and 38°C; 54.4% of them did not describe cough and 76.6% did not report dyspnea. We found a different distribution of the main symptoms (anosmia, ageusia, and cough) among the three groups of patients, except for fever (Table 2).

At t3, we found a significantly higher rate of persisting fever among patients with moderate (76.5% with temperature 37–38°C, 14.8% with temperature ≥38°C) and severe outcomes (42.9% with temperature 37–38°C, 32.5% with temperature ≥38°C) compared to mild COVID-19 outcome (22.8% with temperature 37–38°C, 4.7% with temperature ≥38°C), p < 0.001 (Table 3). At this time point, 25.8% of subjects reported the appearance of a cough, but 81.5% of them still did not experience dyspnea. The dyspnea rate was higher among subjects with severe presentation compared to the other two groups (p < 0.001, Table 3).

Interestingly, at t7, we found the same trend we observed at t3, with 40.3% of subjects with persisting fever ≥38°C among patients with severe COVID-19, compared to 9.9% in moderate and 4.1% in mild groups, p < 0.001 (Table 4). At this specific time point, 18.8% reported cough, and the same percentage reported dyspnea, with higher rates in the group of severe COVID-19 (p < 0.01). Moreover, we described a different distribution of other symptoms among the three groups, with lower frequencies of anosmia and ageusia in patients with severe clinical presentation (p < 0.001 and p = 0.03, respectively).

Figure 1 shows the alluvial diagram of the fever trend from t0 to t7 time points: patients with persistent fever at the first two time points had a higher risk to have the same degree of temperature also in the last time point. On the other hand, patients with a moderate degree of fever (i.e., 37–38°C) at t3 showed a higher probability to achieve a low degree of fever (i.e., 37°C) than achieving a high degree (i.e., ≥38°C). Supporting Information: Figures 1–3 show the river diagrams of fever versus the severity of COVID-19 presentation at t0, t3, and t7, respectively. Patients with a low degree of fever (i.e., 37°C) at t3 had a lower probability to have a severe outcome of COVID-19. The probability of severe outcome increased at t3 and t7. On the other hand, diagrams show that patients with persisting low- or high-grade fever have a higher probability of experiencing a severe outcome.

The multivariate analysis performed via the POLR model (Table 5) showed that factors such as fever 37–38°C (odds ratio [OR], 1.98, 95% confidence interval [CI], 1.01–3.97, p = 0.05), increasing age (OR, 1.05, 95% CI, 1.03–1.07, p < 0.001), and CCI equal to 2–3 points (OR, 3.19, 95% CI, 1.64–6.27, p = 0.001) or ≥4 points (OR, 5.41, 95% CI, 2.35–12.55, p < 0.001) were independently associated with a more severe clinical outcome of COVID-19 at t0 (Model 1). At t3 and t7 (i.e., Models 2 and 3), these results were much stronger: all factors, except for female sex, were associated with a more severe COVID-19 in both time points. At t3, persisting fever represented the factor with the strongest association with severe clinical presentation (37–38°C: OR, 15.34, 95% CI, 7.74–32.44, p < 0.001; ≥38°C: OR, 39.98, 95% CI, 16.78–101.25, p < 0.001). As well, at t7 persisting fever was the main factor associated with a more severe clinical presentation: 37–38°C: OR, 16.76, 95% CI, 7.98–37.19, p < 0.001; ≥38°C: OR, 61.83, 95% CI, 24.69–167.17, p < 0.001. The best model, in terms of performance, was Model 3 (i.e., with fever at t3) according to the AIC, BIC, and pseudo-$R^2$ evaluation criteria. Results did not change when we included only those patients reporting all clinical data at the three different time-points (Supporting Information: Table 1); however, the goodness of fit measures improved.

4 DISCUSSION

COVID-19 can show a wide range of outcomes, from asymptomatic and mild respiratory infections to more severe diseases with ARDS, need for ICU admission, and/or death. However, patients initially
| Age, years | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|------------|----------------|-----------------|----------------|----------------|---------|
| Mean ± SD  | 46.2 ± 15.6    | 56.6 ± 15.6     | 66.2 ± 14.9    | 53.4 ± 17.4    | <0.001  |

| Sex | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-----|----------------|-----------------|----------------|----------------|---------|
| Male | 88 (51.5%)    | 54 (66.7%)      | 40 (51.9%)     | 182 (55.3%)    | 0.130   |
| Female | 83 (48.5%) | 27 (33.3%)      | 37 (48.1%)     | 147 (44.7%)    |         |

| Hospitalized | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|--------------|----------------|-----------------|----------------|----------------|---------|
| No | 135 (78.9%)    | 13 (16.0%)      | 30 (39.0%)     | 178 (54.1%)    | <0.001  |
| Yes | 36 (21.1%)    | 68 (84.0%)      | 47 (61.0%)     | 151 (45.9%)    |         |

| Death | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-------|----------------|-----------------|----------------|----------------|---------|
| No | 156 (91.2%)    | 60 (74.1%)      | 41 (53.2%)     | 257 (78.1%)    | <0.001  |
| Yes | 0 (0%)         | 1 (1.2%)        | 26 (33.8%)     | 27 (8.2%)      |         |

| CCI, points | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-------------|----------------|-----------------|----------------|----------------|---------|
| Median (IQR: 1, 3) | 0 [0, 1.0] | 2.0 [1.0, 3.0] | 3.0 [1.0, 4.0] | 1.0 [0, 3.0] |         |

| CCI group | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-----------|----------------|-----------------|----------------|----------------|---------|
| 0-1 points | 126 (73.7%) | 37 (45.7%)      | 21 (27.3%)     | 184 (55.9%)    | <0.001  |
| 2-3 points | 27 (15.8%) | 24 (29.6%)      | 31 (40.3%)     | 82 (24.9%)     |         |
| ≥4 points | 5 (2.9%) | 17 (21.0%)      | 23 (29.9%)     | 45 (13.7%)     |         |

| Hypertension | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|--------------|----------------|-----------------|----------------|----------------|---------|
| No | 114 (66.7%)    | 35 (43.2%)      | 32 (41.6%)     | 181 (55.0%)    | <0.001  |
| Yes | 54 (31.6%)    | 41 (50.6%)      | 44 (57.1%)     | 139 (42.2%)    |         |

| CVD | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-----|----------------|-----------------|----------------|----------------|---------|
| No | 150 (87.7%)   | 65 (80.2%)      | 51 (66.2%)     | 266 (80.9%)    | <0.001  |
| Yes | 18 (10.5%)    | 15 (18.5%)      | 25 (32.5%)     | 58 (17.6%)     |         |

| COPD | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|------|----------------|-----------------|----------------|----------------|---------|
| No | 167 (97.7%) | 73 (90.1%)      | 67 (87.0%)     | 307 (93.3%)    | 0.003   |
| Yes | 2 (1.2%) | 8 (9.9%)        | 9 (11.7%)      | 19 (5.8%)      |         |

| CKD | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-----|----------------|-----------------|----------------|----------------|---------|
| No | 161 (94.2%) | 74 (91.4%)      | 70 (90.9%)     | 305 (92.7%)    | 0.620   |
| Yes | 7 (4.1%) | 3 (3.7%)       | 6 (7.8%)       | 16 (4.9%)      |         |

| Cancer | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|--------|----------------|-----------------|----------------|----------------|---------|
| No | 165 (96.5%) | 76 (93.8%)      | 70 (90.9%)     | 311 (94.5%)    | 0.240   |
| Yes | 4 (2.3%) | 5 (6.2%)       | 6 (7.8%)       | 15 (4.6%)      |         |

| Cirrhosis | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-----------|----------------|-----------------|----------------|----------------|---------|
| No | 163 (95.3%) | 74 (91.4%)      | 72 (93.5%)     | 309 (93.9%)    | 0.350   |
| Yes | 1 (0.6%) | 0 (0%)         | 2 (2.6%)       | 3 (0.9%)       |         |

| Diabetes mellitus | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|-------------------|----------------|-----------------|----------------|----------------|---------|
| No | 159 (93.0%) | 66 (81.5%)      | 57 (74.0%)     | 282 (85.7%)    | <0.001  |
| Yes | 9 (5.3%) | 15 (18.5%)      | 19 (24.7%)     | 43 (13.1%)     |         |

Abbreviations: CCI, Charlson comorbidity index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular diseases; IQR, interquartile range; SD, standard deviation.
A systematic review and meta-analysis assessed demographic, laboratory, and clinical factors that may predict a severe presentation of COVID-19. In total, 69,762 patients from 88 studies were meta-analyzed, of whom 5,311 died and 2,112 provided information on ICU admission: patients requiring ICU admission and patients who died had a higher median age compared to patients not requiring ICU and to survivors, respectively (65 years, CI, 62.27–66.16, vs. 59 years, CI, 55.93–61.86 and 71 years, CI, 69.3–71.61, vs. 58 years, CI, 55.03–59.4, respectively). Among COVID-19 symptoms, dyspnea, and fatigue were significantly associated with both ICU admission (OR, 5.34, CI, 2.77–10.28 and OR, 1.63, CI, 1.20–2.22, respectively) and death (OR, 3.69, CI, 2.54–5.36 and OR, 1.48, CI, 1.15–1.89, respectively). Regarding comorbidities, patients requiring ICU admission suffered more frequently from cerebrovascular disease (OR, 5.88, CI, 2.35–14.73), hypertension (OR, 1.62, CI, 1.24–2.12), diabetes mellitus (OR, 1.59, CI, 1.29–1.93), and chronic kidney disease (OR, 1.48, CI, 2.91–5.30), cerebrovascular disease (OR, 3.45, CI, 2.42–4.91), chronic lung disease (OR, 3.12, CI, 2.17–4.49), and hypertension

|                | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|----------------|---------------|------------------|----------------|----------------|---------|
| Fever          |               |                  |                |                |         |
| <37°C          | 52 (30.4%)    | 70 (8.6%)        | 15 (19.5%)     | 74 (22.5%)     | 0.063   |
| 37–38°C        | 86 (50.3%)    | 45 (55.6%)       | 37 (48.1%)     | 168 (51.1%)    |         |
| ≥38°C          | 18 (10.5%)    | 11 (13.6%)       | 10 (13.0%)     | 39 (11.9%)     |         |
| Dyspnea        |               |                  |                |                |         |
| No             | 150 (87.7%)   | 54 (66.7%)       | 48 (62.3%)     | 252 (76.6%)    | <0.001  |
| Yes            | 7 (4.1%)      | 9 (11.1%)        | 14 (18.2%)     | 30 (9.1%)      |         |
| Anosmia        |               |                  |                |                |         |
| No             | 123 (71.9%)   | 55 (67.9%)       | 57 (74.0%)     | 235 (71.4%)    | 0.005   |
| Yes            | 33 (19.3%)    | 8 (9.9%)         | 1 (1.3%)       | 42 (12.8%)     |         |
| Ageusia        |               |                  |                |                |         |
| No             | 131 (76.6%)   | 57 (70.4%)       | 57 (74.0%)     | 245 (74.5%)    | 0.032   |
| Yes            | 25 (14.6%)    | 6 (7.4%)         | 1 (1.3%)       | 32 (9.7%)      |         |
| Cough          |               |                  |                |                |         |
| No             | 115 (67.3%)   | 29 (35.8%)       | 35 (45.5%)     | 179 (54.4%)    | <0.001  |
| Yes            | 40 (23.4%)    | 34 (42.0%)       | 27 (35.1%)     | 101 (30.7%)    |         |
| Diarrhea       |               |                  |                |                | 0.260   |
| No             | 147 (86.0%)   | 62 (76.5%)       | 56 (72.7%)     | 265 (80.5%)    |         |
| Yes            | 8 (4.7%)      | 1 (1.2%)         | 6 (7.8%)       | 15 (4.6%)      |         |
| Skin rash      |               |                  |                |                |         |
| No             | 154 (90.1%)   | 62 (76.5%)       | 54 (70.1%)     | 270 (82.1%)    | NA      |
| Yes            | 0 (0%)        | 0 (0%)           | 0 (0%)         | 0 (0%)         |         |

Abbreviations: COVID-19, coronavirus disease 2019; NA, not applicable.
Chronic kidney disease (OR, 2.49, CI, 1.89–2.94), diabetes mellitus (OR, 2.14, CI, 1.82–2.52), and cancer (OR, 2.08, CI, 1.55–2.77) showed increased OR for mortality. Moreover, Xiao et al. in a retrospective study on 690 patients hospitalized with COVID-19 proposed a risk score for the identification of patients with a potentially severe COVID-19, the HNC-LL score, which included hypertension, neutrophil count, CRP, lymphocyte count, and LDH. The score showed a good accuracy (receiver operating characteristic curve >0.85) to predict a severe disease, and a good predictive ability to identify patients admitted to the hospital with mild disease who progressed to a severe presentation during hospitalization. Nevertheless, the timing of the disease, that is, the delay between the onset of symptoms and the hospital admission was not considered. Furthermore, the HNC-LL score needs blood sampling, therefore it may not be useful for nonhospitalized patients.

All the studies in the literature underline the presence of risk factors that may predict a potentially severe COVID-19 in a hospital setting. However, only 15%–25% of all subjects with SARS-CoV-2 infection need hospitalization, and the clinical management of the remaining patients is assigned to primary health care. Indeed, the prediction of COVID-19 clinical presentation in the very early phase of infection in the outpatient setting is urgently needed and may help clinicians and healthcare professionals in recognizing subjects with a higher risk of severe clinical outcomes of the disease, therefore selecting subjects who may benefit from early treatment and/or hospitalization. This is central considering the more recent therapeutic options, i.e., monoclonal antibodies and early antivirals (remdesivir, molnupiravir, and paxlovid), that act in the very early stage of infection reducing the risk of COVID-19 severity.

The present study suggested that patients with persisting fever on Days 3 and 7 after the onset of symptoms or from the first SARS-CoV-2-RNA positivity may potentially have a subsequent severe outcome of the disease, and therefore they should be considered for early antiviral treatment and/or hospitalization. These data seem to be useful for healthcare authorities to better allocate resources in the outpatient setting.

This study has some limitations, that is, the retrospective design, the small sample size of patients, and the study period (until April 2021), since we considered the first three waves of the pandemic. Moreover, patients enrolled in our study were not vaccinated against...
| Symptom | Mild (N = 171) | Moderate (N = 81) | Severe (N = 77) | Total (N = 329) | p-Value |
|---------|----------------|------------------|----------------|----------------|---------|
| Fever | | | | | |
| <37°C | 135 (78.9%) | 15 (18.5%) | 9 (11.7%) | 159 (48.3%) | <0.001 |
| 37–38°C | 16 (9.4%) | 39 (48.1%) | 18 (23.4%) | 73 (22.2%) | |
| ≥38°C | 7 (4.1%) | 8 (9.9%) | 31 (40.3%) | 46 (14.0%) | |
| Dyspnea | | | | | |
| No | 144 (84.2%) | 44 (54.3%) | 27 (35.1%) | 215 (65.3%) | <0.001 |
| Yes | 13 (7.6%) | 18 (22.2%) | 31 (40.3%) | 62 (18.8%) | |
| Anosmia | | | | | |
| No | 112 (65.5%) | 26 (32.1%) | 43 (55.8%) | 181 (55.0%) | <0.001 |
| Yes | 42 (24.6%) | 35 (43.2%) | 13 (16.9%) | 90 (27.4%) | |
| Ageusia | | | | | |
| No | 121 (70.8%) | 49 (60.5%) | 52 (67.5%) | 222 (67.5%) | 0.030 |
| Yes | 33 (19.3%) | 12 (14.8%) | 2 (2.6%) | 47 (14.3%) | |
| Cough | | | | | |
| No | 134 (78.4%) | 40 (49.4%) | 36 (46.8%) | 210 (63.8%) | <0.001 |
| Yes | 21 (12.3%) | 21 (25.9%) | 20 (26.0%) | 62 (18.8%) | |
| Diarrhea | | | | | |
| No | 148 (86.5%) | 57 (70.4%) | 56 (72.7%) | 261 (79.3%) | 0.620 |
| Yes | 6 (3.5%) | 4 (4.9%) | 1 (1.3%) | 11 (3.3%) | |
| Skin rash | | | | | |
| No | 154 (90.1%) | 60 (74.1%) | 53 (68.8%) | 267 (81.2%) | 0.870 |
| Yes | 1 (0.6%) | 0 (0%) | 0 (0%) | 1 (0.3%) | |

Abbreviation: COVID-19, coronavirus disease 2019.

**Figure 1** Alluvial diagram of fever trend from $t_0$ to $t_7$. 
SARS-CoV-2, since the first vaccine distribution across Europe started on December 31, 2020, for healthcare professionals. In particular, in Italy, the National Strategic Plan for the prevention of SARS-CoV2 infection was launched on March 12th, 2021. More multicenter prospective studies including both subjects vaccinated and not vaccinated are urgently needed, to better investigate early predictors of COVID-19 severity in the very early phase of infection.

In conclusion, the early identification of patients at risk for the development of the more severe disease may help clinicians and policymakers in tailoring management strategies for patients with COVID-19 from the very beginning of the infection, allowing rapid access to early treatments and/or the initiation of supportive care treatments. According to the results of the present study, patients with persisting fever on Day 3 and Day 7 should be closely followed-up for clinical deterioration and should require a rapid referral to COVID-19 centers for early antiviral treatment and/or hospitalization. Other studies, including vaccinated patients, are urgently needed to better allocate resources in the decision-making process.

| TABLE 5 | Results obtained by POLR models using as covariates the three different time points of fever |
|---------|----------------------------------|----------------------------------|----------------------------------|
|         | MODEL 1 (t = 0)                  | MODEL 2 (t = 3)                  | MODEL 3 (t = 7)                 |
|         | Lower | Upper | 95% CI | p-Value | Lower | Upper | 95% CI | p-Value | Lower | Upper | 95% CI | p-Value |
| Fever: 37–38°C | 1.98 | 1.01 | 3.97 | 0.050 | 15.34 | 7.74 | 32.44 | 0.000 | 16.76 | 7.98 | 37.19 | 0.000 |
| Fever: ≥38°C | 1.70 | 0.70 | 4.14 | 0.237 | 39.98 | 16.78 | 101.25 | 0.000 | 61.83 | 24.69 | 167.18 | 0.000 |
| Age      | 1.05 | 1.03 | 1.08 | 0.000 | 1.04 | 1.02 | 1.06 | 0.001 | 1.07 | 1.04 | 1.09 | 0.000 |
| Sex: Female | 1.00 | 0.59 | 1.72 | 0.986 | 1.29 | 0.75 | 2.19 | 0.370 | 1.58 | 0.83 | 3.06 | 0.166 |
| Charlson group: 2–3 | 3.19 | 1.64 | 6.27 | 0.001 | 2.47 | 1.25 | 4.92 | 0.009 | 2.23 | 1.05 | 4.74 | 0.036 |
| Charlson group: ≥4 | 5.41 | 2.35 | 12.55 | 0.000 | 4.35 | 1.95 | 9.86 | 0.000 | 4.34 | 1.74 | 11.06 | 0.002 |
| AIC      | 437.32 | 440.05 | 324.53 |
| BIC      | 465.99 | 469.65 | 353.14 |
| McFadden | 0.21  | 0.31  | 0.41  |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; OR, odds ratio; POLR, proportional odds linear regression.

5 | COVICAM GROUP

The members of the groups are Nicola Coppola, Caterina Monari, Caterina Sagnelli, Paolo Maggi, Vincenzo Sangiovanni, Fabio G. Numis, Ivan Gentile, Alfonso Masullo, Carolina Rescigno, Giosuèle Calabria, Angelo S. Megna, Michele Gambardella, Elio Manzillo, Grazia Russo, Vincenzo Esposito, Vincenzo Messina, Mariantonietta Pisaturo, Enrico Allegorico, Biagio Pinchera, Raffaella Pisapia, Mario Catalano, Angela Salzillo, Giovanni Porta, Antonio R. Buonomo, Riccardo Scotto, Biagio Pinchera, Emanuela Zappulo, Giulio Vicente, Nicola S. Moriello, Maria Foggia, Margherita Macera, Federica Calò, Anna M. Rossomando, Viviana Rizzo, Antonio Russo, Nunzia Farella, Giulia Liorre, Laurore Paradiso, Alfonso Liberti, Giorgio Bosso, Claudia Serra, Ferdinando D. Vicario, Valentina Minerva, Vincenzo Selva, Filomena Simeone, Giulia De Angelis, Stefania De Pascalis, and Vincenza Pontillo.

AUTHOR CONTRIBUTIONS

Caterina Monari, Mariantonietta Pisaturo, and Nicola Coppola were involved in the study concept and design and drafting of the manuscript. Mario Fordellone was involved in statistical analysis. Paolo Chiodini was involved in the statistical analysis and in the critical revision of the manuscript. Paolo Maggi, Giovanni Di Caprio, Margherita Macera, and Valeria Gentile were involved in the acquisition of data, analysis, and interpretation of data and in the critical revision of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data may be required from the corresponding author, Prof Nicola Coppola (Nicola.coppola@unicampania.it).
ETHICS STATEMENT
The study was approved by the Ethics Committee of the University of Campania Luigi Vanvitelli, Naples (n°10877/2020, May 11, 2020). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

ORCID
Nicola Coppola http://orcid.org/0000-0001-5897-4949

REFERENCES
1. WHO. Coronavirus disease (COVID-19) pandemic. Accessed February 18, 2022. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. WHO. WHO coronavirus (COVID-19) dashboard. 2022. Accessed February 14, 2022. https://covid19.who.int
3. IDSA. IDSA guidelines on the diagnosis of COVID-19: molecular diagnostic testing. 2020. Accessed February 14, 2022. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/
4. WHO. Therapeutics and COVID-19: living guideline. 2022. 143. Accessed June 8, 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.4
5. Iczovich AI, Alberto Ragusa M, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. PLoS One. 2020;17:e0269291. doi:10.1371/journal.pone.0241955
6. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. Rev Med Virol. 2021;31:1-10. doi:10.1002/jmv.2146
7. Mudatsir M, Fajar JK, Wulandari L, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis. F1000Res. 2021;9:110. doi:10.12688/F1000RESEARCH.26186.2
8. Côté A, Ternacle J, Pibarot P. Early prediction of the risk of severe coronavirus disease 2019: a key step in therapeutic decision making. EBioMedicine. 2020;59:102948. doi:10.1016/j.ebiom.2020.102948
9. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573-577. doi:10.7326/0003-4819-147-8-20070116-00010
10. NIH. Clinical spectrum of SARS-CoV-2 infection. 2021. Accessed February 14, 2022. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
11. WHO. Living guidance for clinical management of COVID-19. 2021. Accessed February 14, 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
12. Ross A, Willson V. One-way ANOVA. Basic and Advanced Statistical Tests. Brill; 2017.
13. McGhie PE, Najab J. Kruskal-Wallis test. The Corsini Encyclopedia of Psychology. John Wiley & Sons; 2010.
14. Royston JP. Some techniques for assessing multivariate normality based on the Shapiro-Wilk W. J Roy Stat Soc: Ser C (Appl Stat). 1983;32:121-133
15. Plackett RL. Karl Pearson and the chi-squared test. Int Stat Rev. 1983;51:59-72.
16. Brant R. Assessing proportionality in the proportional odds model for ordinal logistic regression. Biometrics. 1990;46:1171-1178.
17. Veall MR. Zimmermann KF. Pseudo-R² measures for some common limited dependent variable models. J Econ Surv. 1996;10(3):241-259.
18. Russo A, Minichini C, Starace M, Astorri R, Calò F, Coppola N, Vanvitelli COVID-19 group. Current status of laboratory diagnosis for COVID-19: a narrative review. Infect Drug Resist. 2020;13:2657-2665. doi:10.2147/IDR.S264020
19. Cecconi M, Piovani D, Brunetta E, et al. Clinical medicine early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in Lombardy, Italy. J Clin Med. 2020;9(5):1548. doi:10.3390/jcm9051548
20. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China supplemental content. JAMA Intern Med. 2020;180(7):934-943. doi:10.1001/jamainternmed.2020.0994
21. Sharma J, Rajput R, Bhatia M, Arora P, Sood V. Clinical predictors of COVID-19 severity and mortality: a perspective. Front Cell Infect Microbiol. 2021;11(October):674277. doi:10.3389/fcimb.2021.674277
22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
23. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7
24. Monari C, Sagnelli C, Maggi P, et al. More severe COVID-19 in patients with active cancer: results of a multicenter cohort study. Front Oncol. 2021. doi:10.3389/fonc.2021.662746
25. Katzenschlager S, Zimmer AJ, Gottschalk C, et al. Can we predict the severe course of COVID-19—a systematic review and meta-analysis of indicators of clinical outcome? PLoS One. 2021;16:e0255154. doi:10.1371/journal.pone.0255154
26. Xiao LS, Zhang WF, Gong MC, et al. Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019. EBioMedicine. 2020;57:102880. doi:10.1016/j.ebiom.2020.102880
27. NIH. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2022. Accessed June 8, 2022. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
28. EpiCentro I. Vaccines & Immunizations. 2021. Accessed February 14, 2022. https://www.epicentro.iss.it/en/vaccines/covid-19-vaccination-plan

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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