SARS-COV-2 comorbidity network and outcome in hospitalized patients in Crema, Italy

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Abstract

Background
No systematic data on hospitalized Covid-19 patients from Western countries are available

Objective
To detail onset, course, correlations with comorbidities and sensitivity of nasopharyngeal swab.

Design
Prospective cohort study

Setting
Hospital-based study

Participants
539 consecutive individuals suspected to carry Covid-19

Intervention
All individuals underwent clinical and laboratory exams, SARS-COV-2 assay on nasopharyngeal swab, and chest X-ray and/or computed tomography (CT). Data on onset, course, comorbidities, number of drugs including angiotensin converting enzyme inhibitors and angiotensin-II-receptor antagonists, follow-up swab, pharmacological treatments, non-invasive respiratory support, ICU admission, and deaths were recorded.

Measurements
Need of non-invasive respiratory support, ICU admission, death.

Results
Median age of 411 Covid-19 patients was 70.5 years (range 1-99; 66.6% males). CT was positive in 74% and negative in 3.2%. Six patients died within 72 hours; another 66 during hospitalization. Fatality rate was 17.5% (74% males). No death occurred below 60 years. Mortality was 6.6% in 60-69 decade, 21.1% in 70-79, 38.8% in 80-89, and 83.3% above 90 years. Non-invasive respiratory support rate was 27.2%; ICU admission 6.8%. Older age, cough and dyspnea at onset, hypertension, cardiovascular diseases, diabetes, renal insufficiency, >7 drugs intake and positive X-ray at admission were significantly associated with death. Low lymphocyte count, high C-reactive protein, aspartate aminotransferase and lactate dehydrogenase, and low PO\(_2\) partial pressure with high lactate at arterial blood gas analysis at admission were significantly associated with death. Of 32 swab negative patients, 40.6% turned positive at follow-up. Using CT as reference, nasopharyngeal swab had 80% sensitivity. Comorbidity network analysis revealed homogenous distribution of deceased and 60-80 aged patients across diseases.

Conclusion
Covid-19 caused high mortality among patients older than 70 years and correlated by pre-existing multiorgan impairment irrespective of the age.
Introduction

Since December 2019 outbreak in China of the novel coronavirus infection, designated SARS-CoV-2 and termed Covid-19, the disease has quickly overflowed worldwide, to date mostly affecting the European countries and the United States. Covid-19 causes a clinical syndrome encompassing asymptomatic or oligosymptomatic flu-like course, gastrointestinal disturbances, mild pneumonia, acute respiratory distress and death. (1-3)

After the first Italian patient was recorded nearby Crema, the total number of Covid-19 patients in the Lombardy Region exponentially increased every 10 days to about 1,000, 10,000, and more than 30,000 on March 25th. The municipality of Crema, with about 34,000 inhabitants, experienced a rapid overload of the healthcare structures due to a massive influx of suspected Covid-19 patients.

We sought to perform a systematic analysis of hospitalized Covid-19 patients after outbreak in Italy and outline possible correlations with known diseases and their treatment. To this aim, we investigated all consecutive individuals suspected to harbor Covid-19 and admitted at the General Hospital of Crema between February 21st and March 13th, 2020. We provided data on onset, clinical history, and course of the disease during the first 72 hours and ensuing hospitalization, age and sex-stratified fatality rate, and diagnostic accuracy of the nasopharyngeal swab. We applied a network analysis to assess the interactions between comorbidities across age groups and outcomes.

We trust our findings can provide the global community and healthcare systems with useful information to better face the current health emergency and identify novel strategies to prevent worst outcomes in patients.

Methods

On February 19th, the General and Health Directorate of the Hospital of Crema met to update and carry out the available procedures to cope with the hospitalization of patients with a potential viral spread, based on 2009 SARS and H1N1 pandemic strategic plan revised on December 2014 after Ebola outbreak. Starting on February 21st, the Emergency Department set up a triage for any individual either reporting or presenting with fever, cough or dyspnea, or having had contact with Covid-19 carriers. The Institutional Review Board has approved the study.

Since February 21th, all suspected individuals admitted to the hospital underwent body temperature and pulse oximetry (SO2) recording, hematological screening, chest X-ray and/or computed tomography (CT) and nasopharyngeal swab. Swabs were stored at +4°C and immediately shipped to one of the laboratory of virology accredited by the Lombardy Region for diagnostic SARS-COV-2 real-time polymerase chain reaction assay. Based on clinical, laboratory and radiological findings, patients were discharged to home in quarantine or hospitalized.
Demographic data, date of onset and type of symptoms, comorbidities (e.g. hypertension, cardiovascular disorders, diabetes, pulmonary diseases, active and previous malignancies, renal insufficiency and any other known condition), current pharmacological treatments, use of angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin-II-receptor antagonists (sartans), and number of drugs were recorded. All available clinical data during the first 72 hours and ensuing hospitalization, including hematological and radiological exams, antiviral treatment, respiratory support with continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV), ICU admission and deaths were recorded. Chest X-ray and CT scan were scored as positive or negative based on radiologists’ written report. Acute reticular pattern at X-ray and the presence of single or multiple ground-glass and/or consolidative lung opacities were considered suggestive of interstitial pneumonia. Pleural and pericardial effusion, and lymphadenopathy at CT scan were recorded. Follow-up data were recorded until March 19th.

The hospital of Crema is fully equipped with a computerized recording system that generates a unique code for any visit and exam. All patients were anonymized and locked to the unique code assigned at the admission, and all data were included in an electronic database.

Comorbidity network analysis

Comorbidity network(4) has been obtained by firstly dividing the cohort of Covid-19 patients in three classes based on the year of birth: 1920-1940 1941-1960 and 1961-1980. The network was calculated as the projection of the patient-disease bipartite network on the diseases space. A bipartite network comprises a set of graph nodes decomposed into two disjoint sets A and B, such that no two-graph vertices within the same set are adjacent. This means that only edges connecting vertices in A to those in B are considered. The A-projection is composed of a network containing only A-nodes, where two A-nodes are connected when they have at least N common neighboring B-node.(5) The final monopartite disease network resulted by fixing N to the 10% of the number of patients included in each class. The three comorbidity networks have been analyzed in terms of nodes weighted degree(6) and modularity.(7) Thereafter, the same cohort was divided in deceased and survived patients. Comorbidity networks were obtained for the two groups in the same way described above and the same topological analysis was performed.

Statistical analysis

Descriptive statistics were provided in terms of absolute number and percentage for categorical data, and mean with standard deviation (SD) and median with value range for continuous data. Differences between groups were assessed by the chi-square test or Mann-Whitney test, as appropriate; Bonferroni correction was used to adjust for multiple testing. Sensitivity and specificity with the corresponding 95% confidence interval (95% CI), and positive and negative predicting values of the nasopharyngeal swab were calculated using as reference the CT scan.
Comorbidity network has been analyzed by dividing the patients in three classes of age and outcome (deceased and survived) at last day of follow-up. For each group, the comorbidity network was derived according to the constraint that at least 10% of patients must share two diseases.

**Data availability and sharing**

The data that support the findings of this study are available from the corresponding author.

**Results**

**Clinical features of the study population**

Between February 21th and March 13th, of the 2,217 admitted to the Emergency Department, 766 (34.5%) Covid-19 suspected individuals underwent the triage. Of them, 297 (38.8%) arrived with an ambulance and 469 (61.2%) with their own means.

Nasopharyngeal swab result was available within 24 hours on average. Of the 766 patients admitted, 419 (54.7%) were positive, 312 (40.7%) were negative, and 35 (5.6%) had no report yet. Eight positive patients were not included in the analysis because of missing data: 3 were admitted for acute myocardial infarction (1 died and 1 moved to another hospital), and 1 for hemorrhagic stroke; no data were available for the other 4 patients. Eventually, we could collect relevant data from 411 Covid-19 and 128 swab negative consecutive patients, which represented our study population.

The mean time to admission after onset of symptoms was 5.3±4.3 days in Covid-19 and 5.7±4.1 days in swab negative patients. The frequency of fever, cough and dyspnea did not differ between groups. About 4% of patients reported gastrointestinal symptoms, with similar distribution between groups (table 1). Anosmia and ageusia were not systematically investigated.

Thirteen patients arrived in coma. Of them, 9 were Covid-19 patients and 5 died. The other 4 patients were negative; 3 died and 1 was hospitalized. Another 21 patients presented with disorientation and/or with psychomotor restlessness; 15 were Covid-19 patients and 2 died. The other 6 patients were swab negative and 4 died. Notably, 41 (9.9%) Covid-19 patients reported or had at arrival one or more syncope; 14 of them had a fall with trauma and 5 died. Another 6 (4.7%) swab negative patients reported syncope and 1 died.

At admission, body temperature was slight above 37°C both in Covid-19 and swab negative patients. Nevertheless, the large majority of patients reported the intake of paracetamol during the previous hours, thus influencing the assessment at arrival. Similarly, the mean value of pulse oximetry in patients who arrived in ambulance was influenced by the early treatment with oxygen mask during transportation. The mean value of those who reached the hospital by their own means did not differ between Covid-19 (93%, range 60-100) and swab negative (92%, range 50-100) patients.
The rapidly increasing number of patients needing respiratory support required a fast reorganization of the entire hospital. In particular, the number of sub-intensive care beds to assist patients with CPAP and NIV was increased by 324% and that of ICU beds by 100% (fig. 1).

**Course and outcome in Covid-19 patients**

The median age was 70.5 years (range 1-99), with a preponderance of males (66.6%). One 87 year-old had confusion, psychomotor restlessness, vomit and fever; he arrived in coma with 38.5°C of body temperature and stiff neck, and died after 3 days with diagnosis of possible meningoencephalitis.

Of 411 patients, 262 (63.7%) were hospitalized, 44 (10.7%) were transported to other regional hospitals, and 16 (3.9%) were discharged to home in quarantine.

Chest X-ray was performed in 128 (31.1%) patients; it was reported as possibly/probably positive in 79 (19.2%) patients and negative in 49 (11.9%). CT was performed in 317 (77.2%) patients; it was reported as positive in 304 (74%) and negative in 13 (3.2%). It showed pleural effusion in 29 (9.1%) patients, lymphadenopathy in 37 (11.7%), and pericardial effusion in 27 (8.5%). Of the 38 (9.2%) patients who underwent both the exams, 31 (81.6%) had concordant positive report, 6 (15.8%) had positive CT scan and negative X-Ray report, and 1 (2.6%) had negative CT scan and positive X-Ray report (table 2).

Laboratory exams at admission showed white blood cell count below 10x10^9/L in 82% of patients, neutrophil count below 10x10^9/L in 83.4%, and lymphocyte count below 1x10^9/L in 55.6%. C-reactive protein was mildly elevated in most patients, particularly those with worst clinical picture and outcome. Aspartate aminotransferase and lactate dehydrogenase values were relatively higher than creatinine and creatine kinase (table 3).

Six patients died within the first 72 hours and another 66 during the ensuing hospitalization, giving an overall fatality rate of 17.5%. No death occurred in patients aged below 60 years. In the older age groups, the number of deaths was 26 (88.5% males) in the decade 70-79 and 31 (71% males) in the decade 80-89 (fig. 2). Non-invasive respiratory support was needed in 112 (27.2%) patients, with 28 (6.8%) requiring ICU admission.

Antiretroviral treatment with ritonavir plus lopinavir was started in 42.3% of patients, in combination with hydroxychloroquine sulfate in 63% of them.

**Course, outcome and follow-up nasopharyngeal swab in negative patients**

The median age was 67.7 years (range 1-98), with a preponderance of males (63.3%). Thirty-six (28.1%) patients arrived at hospital with an ambulance. One 36 year-old woman with recurring epileptic seizures and possible meningoencephalitis was moved to another hospital. Seven patients (78 to 97 years) died; CT scan could be performed in 5 and was positive in all.

Of 128 patients, 82 (64%) were hospitalized and 25 (19.5%) were discharged to home in quarantine. None was moved to other regional hospitals.
Chest X-ray was performed in 59 (46%) patients; it was reported as possibly/probably positive in 30 (23.4%) and negative in 29 (22.7%). CT scan was performed in 122 (95.3%) patients, and was reported as positive in 76 (69.4%) and negative in 11 (12.6%). It showed pleural effusion in 6 (6.9%) patients, lymphadenopathy in 8 (6.2%), and pericardial effusion in 41 (32%). Of the 21 (16.4%) patients who underwent both the exams, 16 (76.2%) had concordant positive report, 3 (14.3%) had positive CT scan and negative X-Ray report, and 2 (9.5%) had concordant negative report.

Laboratory exams at admission showed white blood cell count below 10x10⁹/L in 61% of patients, neutrophil count below 10x10⁹/L in 67.4%, and lymphocyte count below 1x10⁹/L in 32.2%. C-reactive protein was mildly elevated in most patients, particularly those with worst clinical picture and outcome. Aspartate aminotransferase and lactate dehydrogenase values were relatively higher than creatinine and creatine kinase in most patients.

Two patients died within the first 72 hours and another 15 during hospitalization, giving an overall fatality rate of 13.3%. Nine (53%) of the 17 patients who died had positive CT scan as compared to 25 (22.5%) in those hospitalized or discharged. Non-invasive respiratory support was needed in 22 (17.2%) patients, with 4 (3.1%) requiring ICU admission.

Antiretroviral treatment with ritonavir plus lopinavir was started in 27 (42.3%) patients, in combination with hydroxychloroquine sulfate in 82.1% of them.

Of 128 patients, 32 (25%) repeated the testing (median time 8 days, range 1-26) and 13 (40.6%) turned positive. Eight (61.5%) had either X-ray or CT positive, none was admitted in ICU, and 3 died during hospitalization.

**Diagnostic accuracy of nasopharyngeal swab**

The result of the nasopharyngeal swab did not influence the risk of any event included in the primary outcome. Therefore, we used as reference the report of chest CT to calculate the diagnostic accuracy of the nasopharyngeal swab. The sensitivity was 0.80 (CI 0.76-0.84), the specificity was 0.45 (CI 0.25-0.65), the positive predicting value was 0.96, and the negative predictive value was 0.13.

**Comorbidity pattern and risk profile for outcome in Covid-19 patients**

Older age, cough and dyspnoea at onset, history of hypertension, cardiovascular diseases, diabetes, renal insufficiency, intake of 7 or more drugs and positive chest X-ray at admission were significantly associated with death (table 2). Among laboratory exams at admission, low lymphocyte count, high C-reactive protein, aspartate aminotransferase and lactate dehydrogenase, and low PO₂ partial pressure with high lactate at arterial blood gas analysis were also significantly associated with death (table 3).

Comorbidity network analysis was performed on the whole cohort of Covid-19 patients born between 1920 and 1980, and suffering for at least one of the diseases included in the analysis. Subsequently, the reduced sample was divided in three age groups: 1920-1940, 1941-1960 and 1961-1980. The comorbidity networks
obtained from those groups (fig. 3 a, b and c) showed different topological properties. The community detection algorithm was able to identify two modules only for the age groups 1920-1940 and 1961-1980, whereas only one community characterized the age group 1941-1960. It means that in the two extremes of the range of age there are two different groups of diseases (pink and green in fig. 3 a and c) and the number of patients who share two diseases is more similar between two nodes of the same community than between two nodes of different communities. Conversely, the one community configuration found in the 1941-1960 age group is associated with a homogeneous distribution of the number of patients who share two diseases across the whole network. The different weighted degree (i.e. the node size) highlights a bimodal disease distribution among patients. Specifically, cardiovascular disease (CaD), respiratory diseases (ReD), diabetes and hypertension (HT) seem to be more largely present among patients, along with chronic renal insufficiency (Rel) and cancer in the 1920-1940 group, cancer in the 1941-1960 group and asthma in the 1961-1980 group. Finally, the same set of patients included in the analysis was divided in two groups according to the outcome deceased or survived. Notably, only one module characterizes the deceased network, whereas the survived network showed two communities. It means that deceased patients were more homogeneously distributed across diseases than survived patients. The weighted degree distribution shows that deceased patients shared equally six important conditions: CaD, ReD, cancer, HT, diabetes and Rel. At the same time, survived patients show the same set of diseases as the most common across patients except Rel (fig. 3 d and e).

Discussion
We report the first systematic analysis of Covid-19 hospitalized patients in Italy since disease outbreak. The strength of our study was the availability of homogenous data from all consecutive patients admitted to the hospital. Indeed, the immediate adoption of the procedures for the hospitalization of patients with a potential viral spread made the Emergency Department ready to apply a standardized triage of all patients suspected to carry Covid-19 infection.

We could follow-up 411 positive patients and compare their clinical features and course to that of 128 patients negative at nasopharyngeal swab. Overall, the percentage of Covid-19 patients that arrived at hospital with an ambulance and required non-invasive respiratory support or ICU admittance was as twice as that of swab negative patients. Nevertheless, the fatality rate was only about 4% higher in Covid-19 patients. At the same time, chest CT was reported as positive in nearly 60% of swab negative patients, as previously reported,(8) and mainly among those who died. It suggests that at least a number of false negative was likely treated. Previous studies reported that nasopharyngeal swab could be negative in patients eventually diagnosed with Covid-19.(9, 10) Our findings could be explained by the 80% sensitivity of swab testing at admission that we calculated using chest CT as reference. Moreover, nearly 41% of
patients negative at admission turned positive at the second testing, while chest X-ray or CT was positive in 61.5% of them.

We chose as primary outcomes non-invasive ventilation (CPAP/NIV), ICU admission and death, to provide information useful for clinical purposes and healthcare planning. Indeed, the effects of the overload of hospitals are intertwined at both levels. For example, the limited availability of CPAP and NIV, and ICU beds compared to the massive request could influence the fatality rate.

Covid-19 predominantly affects males. Our rate of 66.6% males confirmed those reported in China ranging between 54.3% and 73%. (1-3, 11-14) Only one study(15) showed an inverse trend with 56% females affected. No biological explanation for this unexpected gender distribution is currently available.

Fatality rate related to the whole population of Covid-19 subjects is unreliable and of limited usefulness in the pandemic, while urgent strategies are needed to improve patients' care and healthcare system capability. Indeed, the number of Covid-19 subjects experiencing mild, or non-respiratory symptoms (e.g. gastrointestinal), plus those asymptomatic are unknown because of the variability in testing policies. Since hospitalized patients carry the highest risk of dismal outcome, the inherent fatality rate should be used also to compare findings across countries.

Our overall fatality rate was 17.5%. Previous Chinese studies on hospitalized patients reported fatality rates of 28% in 191 patients(12) and 21.8% in 201 patients.(14) Three studies including 99,(1) 137,(15) and 41(2) patients reported lower rates ranging between 11%(1, 15) and 14.6%. (2) Another two studies reported much lower rates of 1.4%(11) and 4.3%.(3) We did not record any death below 60 years. Mortality increased across the decades and it was 6.6% in 60-69 years, 21.1% in 70-79 years, 38.8% in 80-89 years and 83.3% above 90 years. Nearly 74% of the deaths occurred in males, which may be not surprising based on the predominantly male distribution of the diseases. Nevertheless, the fatality rate among males exceeded by 10% that of the whole population of Covid-19 patients, suggesting that the disease could more severely affect males. A similar difference between deaths and infected was reported in one(12) out of three previous studies.(13, 14) Because no previous study provided age-stratified fatality rates, new studies are needed to compare our findings.

Non-invasive respiratory support was needed in 27% of patients and ICU admission rate was 6.8%. Previous Chinese studies(1-3, 15) reported ICU admission rates between 4.3% and 31.7%, with fatality rate between 11% and 14.6%. This comparison may suggest that a larger availability of ICU beds, assumed by higher rates since the actual number of beds was not reported, might be associated with lower fatality rates. To investigate this hypothesis, we analyzed the distribution of the fatality rates in the decades 60-69 (76 patients) and 70-79 (123 patients) (fig. 2). The proportion of patients in CPAP/NIV and ICU (32.9% and 6.5% in 60-69, respectively and 36.5% and 8.1% in 70-79, respectively) did not differ. Nevertheless, the fatality rate was 30% higher in the 70-79 (47%; 21/45; p=0.02) than 60-69 decade (16%; 4/25). Similarly, the fatality rate in ICU was 40% (4/10) in the 70-79 and 0% (0/5) in the 60-69 decade.
Tentative explanation of this large difference could be the generic higher risk related to aging, because the two decades seemed to do not significantly differ in terms of distribution of comorbidities and more than 4 drug intake (10% and 5% higher in 70-79 decade, respectively). Thus, even though it might be possible that higher ICU admission rate could have reduced the mortality in the older age group, leading to a lower overall fatality rate, older age per se might also play a major role on dismal outcome.

All previous studies(1-3, 11-17) reported high frequency of comorbidities mainly among patients with poorer outcome, suggesting a role in enhancing Covid-19 morbidity.(18) To better correlate relationship and frequency of comorbidities to age and outcome, we adopted a network analysis approach. Our findings showed that in deceased patients, six conditions with intrinsic potentiality to induce multiorgan involvement (i.e. CAD, ReD, cancer, HT, diabetes and Re) were equally weighted as compared to surviving patients. The same homogeneous distribution was found in the age group between 60 and 80 years, in which deaths were 43% (31/72) of the total recorded. Even though indirectly, these findings seem confirming the hypothesis that Covid-19 morbidity is enhanced, and possibly even triggered by pre-existing multiorgan impairment, irrespective of the age.(18)

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### Table 1: Distribution of beds before and after Covid-19 emergency

| Department                  | before | %    | beds | % beds Covid-19 | beds | % beds Covid-19 | Delta % |
|-----------------------------|--------|------|------|-----------------|------|-----------------|---------|
| Internal Medicine           | 144    | 35%  | 168  | 69%             | 31   | 51%             | 38%     |
| Sub-intensive Care          | 17     | 4%   | 63   | 26%             | 9    | 18%             | 22%     |
| Intensive Care Unit         | 6      | 1%   | 12   | 5%              | 0    | 3%              | 100%    |
| Surgery                     | 98     | 24%  | 25   | 0%              | 12   | 3%              | -74%    |
| Rehabilitation              | 75     | 18%  | 0    | 0%              | 15   | 4%              | -86%    |
| Maternity and Pediatric     | 19     | 13%  | 0    | 0%              | 5    | 0%              | 0%      |
| Psychiatry                  | 21     | 2%   | 1    | 0%              | 7    | 2%              | 0%      |
| Dialysis                    | 20     | 5%   | 0    | 0%              | 20   | 5%              | 0%      |
| Total                       | 407    | 100% | 244  | 100%            | 146  | 100%            |         |

### Figure 1

**A** Distribution of beds before and after Covid-19 emergency.

**B** Daily number of access to the Emergency Department between February 21 and March 13, 2020.
Figure 2. Age and sex-stratification of the outcomes (CPAP/NIV, ICU admission, and death) in 411 Covid-19 patients. Bars are number of patients. Females are represented in the upper softer bars.
A cohort of 270 Covid-19 patients was firstly divided in three classes according to the year of birth: a) 1920-1940, b) 1941-1960, c) 1961-1980. Subsequently, the cohort was divided in two groups according to the outcome: d) deceased, e) survived. For each group a comorbidity network was derived according to the constraint that at least 10% of patients must share two diseases. The node size relates to the number of connection each disease has with other nodes weighted by the number of patients sharing that disease. The color of each node refers to the community a disease belongs to. Specifically, a), c) and e) showed two different communities of diseases, whereas b) and d) are characterized by one module.
|              | Positive (411) | Negative (128) |
|--------------|----------------|---------------|
| **Arrival at hospital** |                |               |
| Ambulance    | 196 (47.7)     | 36 (28.1)     |
| Own means    | 215 (52.3)     | 92 (71.9)     |
| **Fever**    | 346 (84.2)     | 97 (75.8)     |
| Cough        | 151 (36.7)     | 44 (34.4)     |
| Dyspnoea     | 131 (31.9)     | 34 (26.6)     |
| Syncope      | 41 (9.9)       | 6 (4.7)       |
| **Fall with trauma** | 23 (5.6)       | 7 (5.4)       |
| Nausea       | 18 (4.4)       | 5 (3.9)       |
| Vomit        | 16 (3.9)       | 8 (3.7)       |
| Diarrhoea    | 15 (3.6)       | 5 (3.9)       |
| Confusion/psychomotor restlessness | 15 (3.6)       | 6 (4.7)       |
| Headache     | 10 (2.4)       | 2 (1.6)       |
| Coma         | 9 (2.2)        | 4 (3.1)       |
| Diffuse myalgia/arthralgia | 7 (1.7)       | 2 (1.6)       |
| Thoracic pain| 7 (1.7)        | 10 (7.8)      |
| Abdominal pain | 5 (1.2)     | 2 (0.9)       |
| Pharyngodinia| 4 (1.0)        | 7 (5.4)       |
| **Recent pneumonia in treatment** | 4 (1.0)       | 3 (2.3)       |

*Table 1 Way of arrival at the hospital and symptoms reported by Covid-19 and swab negative patients.*
Table 2 Variables predicting the events included in the primary outcomes (CPAP/NIV, ICU and death) in Covid-19 patients admitted to the Hospital of Crema between February 21 and March 13, 2020, and followed up until March 19, 2020. X-ray and CT are intended as the first exam performed. Sums do not add up to the total because of some missing values. In bold Bonferroni adjusted significant p-values (i.e. p-values<0.017)

| Variable                      | All patients (411) | Deaths (72) | p value | ICU (28) | p value | CPAP/NIV (112) | p value |
|-------------------------------|--------------------|-------------|---------|----------|---------|----------------|---------|
| **Age**                       |                    |             |         |          |         |                |         |
| mean (standard deviation)     | 66.8 (16.4)        | 81.1 (7.5)  | <0.001  | 65.7 (12.1) | 0.24    | 70.9 (10.9)    | 0.03    |
| median (range)                | 70.5 (1-99)        | 80.7 (63-99)|         | 69.1 (33-85)|        | 72.1 (33-91)   |         |
| **Sex, n (%)**                |                    |             |         |          |         |                |         |
| Male                          | 359 (66.6)         | 53 (73.6)   | 0.23    | 26 (92.9) | 0.003   | 91 (81.3)      | <0.001  |
| Female                        | 180 (33.4)         | 19 (26.4)   |         | 2 (7.1)  |         | 21 (18.7)      |         |
| **Cough, n (%)**              |                    |             |         |          |         |                |         |
|                               | 151 (36.7)         | 8 (11.1)    | <0.001  | 11 (39.3) | 0.77    | 33 (29.5)      | 0.06    |
| **Dyspnoea, n (%)**           |                    |             |         |          |         |                |         |
|                               | 131 (31.9)         | 39 (54.2)   | <0.001  | 22 (78.6) | <0.001  | 67 (59.8)      | <0.001  |
| **Any comorbidity, n (%)**    |                    |             |         |          |         |                |         |
|                               | 256 (62.3)         | 61 (84.7)   | <0.001  | 23 (82.1) | 0.03    | 87 (77.7)      | <0.001  |
| Hypertension                  | 193 (47.0)         | 48 (66.7)   | <0.001  | 20 (71.4) | 0.007   | 67 (59.8)      | 0.001   |
| Cardiovascular diseases       | 93 (22.6)          | 28 (38.9)   | <0.001  | 9 (32.1)  | 0.21    | 37 (33.0)      | 0.002   |
| Diabetes                      | 67 (16.3)          | 25 (34.7)   | <0.001  | 7 (25.0)  | 0.20    | 33 (29.5)      | <0.001  |
| Pulmonary diseases            | 48 (11.7)          | 10 (13.9)   | 0.52    | 5 (17.9)  | 0.29    | 18 (16.1)      | 0.09    |
| Renal insufficiency           | 22 (5.3)           | 11 (15.3)   | <0.001  | 5 (17.9)  | 0.002   | 11 (9.8)       | 0.014   |
| Malignancies                  | 33 (8.0)           | 9 (12.5)    | 0.12    | 2 (7.1)   | 0.86    | 8 (7.1)        | 0.69    |
| **Number of drugs, n (%)**    |                    |             |         |          |         |                |         |
| 0                             | 124 (33.9)         | 10 (15.9)   | <0.001  | 4 (16.0)  | 0.03    | 19 (19.0)      | <0.001  |
| <3                            | 89 (24.3)          | 8 (12.7)    |         | 5 (20.0)  |         | 20 (20.0)      |         |
| 4-6                           | 74 (20.2)          | 14 (22.2)   | <0.001  | 5 (20.0)  |         | 25 (25.0)      |         |
| >7                            | 79 (21.6)          | 31 (49.2)   |         | 11 (44.0) |         | 36 (36.0)      |         |
| ACE inhibitors, n (%)         |                    |             |         |          |         |                |         |
|                               | 50 (12.2)          | 11 (15.3)   | 0.37    | 4 (14.3)  | 0.72    | 20 (17.9)      | 0.03    |
| Sartans, n (%)                | 60 (14.6)          | 14 (19.4)   | 0.20    | 9 (32.1)  | 0.006   | 22 (19.6)      | 0.08    |
| **X-Ray, n (%)**              |                    |             |         |          |         |                |         |
| probable/possible             | 79 (19.2)          | 25 (34.7)   | <0.001  | 11 (39.3) | 0.013   | 28 (25.0)      | 0.003   |
| negative                      | 49 (11.9)          | 3 (4.2)     |         | 1 (3.6)   |         | 4 (3.6)        |         |
| not done                      | 283 (68.9)         | 44 (61.1)   |         | 16 (57.1) |         | 80 (71.4)      |         |
| **CT scan, n (%)**            |                    |             |         |          |         |                |         |
| positive                      | 304 (74.0)         | 50 (69.4)   | 0.07    | 23 (82.1) | 0.46    | 92 (82.1)      | 0.019   |
| negative                      | 13 (3.2)           | 0 (0.0)     |         | 0 (0.0)   |         | 0 (0.0)        |         |
| not done                      | 94 (22.8)          | 22 (30.6)   |         | 5 (17.9)  |         | 20 (17.9)      |         |
|                  | All patients (411) | Deaths (72) | p value | ICU (28) | p value | CPAP/NIV (112) | p value |
|------------------|-------------------|-------------|---------|----------|---------|----------------|---------|
| White blood cell count, x 10⁹ per L, n (%) |                   |             |         |          |         |                |         |
| <4               | 56 (14.6)         | 3 (4.8)     | <0.001  | 0 (0.0)  | 0.02    | 5 (4.6)        | <0.001  |
| 4-10             | 281 (73.0)        | 43 (68.2)   |         | 20 (74.1)|         | 77 (71.3)      |         |
| >10              | 48 (12.5)         | 17 (27.0)   |         | 7 (25.9) |         | 26 (24.1)      |         |
| Neutrophil count, x 10⁹ per L, n (%) |                   |             |         |          |         |                |         |
| <7.5             | 321 (83.4)        | 41 (65.1)   | <0.001  | 16 (59.3)| <0.001  | 71 (65.7)      | <0.001  |
| >7.5             | 64 (16.6)         | 22 (34.9)   |         | 11 (40.7)|         | 37 (34.3)      |         |
| Lymphocyte count, x 10⁹ per L, n (%) |                   |             |         |          |         |                |         |
| <1               | 214 (55.6)        | 45 (71.4)   |         | 18 (66.7)| 0.23    | 69 (63.9)      | 0.04    |
| >1               | 171 (44.4)        | 18 (28.6)   |         | 9 (33.3) |         | 39 (36.1)      |         |
| C-reactive protein, g/L, mean (SD) | 7.51 (7.1)       | 13.2 (8.4)  | <0.001  | 15.8 (8.8)| <0.001  | 12.9 (7.9)     | <0.001  |
| Creatinine, mg/dl |                   |             |         |          |         |                |         |
| <1.3             | 283 (73.9)        | 29 (45.3)   | <0.001  | 14 (51.8)| 0.01    | 70 (64.8)      | 0.01    |
| >1.3             | 100 (26.1)        | 35 (54.7)   |         | 13 (48.2)|         | 38 (35.2)      |         |
| Alanine aminotransferase, U/L |                   |             |         |          |         |                |         |
| <40              | 272 (71.8)        | 53 (76.8)   | 0.30    | 15 (55.6)| 0.05    | 64 (54.3)      | 0.001   |
| >40              | 107 (28.2)        | 16 (23.2)   |         | 12 (44.4)|         | 44 (40.7)      |         |
| Aspartate aminotransferase, U/L |                   |             |         |          |         |                |         |
| <37              | 157 (40.5)        | 14 (20.3)   | <0.001  | 3 (11.1) | 0.001   | 16 (14.7)      | <0.001  |
| >37              | 231 (59.5)        | 55 (79.7)   |         | 24 (88.9)|         | 93 (85.3)      |         |
| Lactate dehydrogenase, U/L, mean (SD) | 470 (839.3) | 789 (1710) | <0.001  | 988 (2064)| 0.011   | 636 (1140)     | <0.01   |
| Creatine kinase, U/L, mean (SD) | 401.5 (972.3)    | 650 (1660) | 0.20    | 319 (256)| 0.19    | 409 (1039)     | 0.57    |
| Arterial blood gas |                   |             |         |          |         |                |         |
| pO2 partial pressure, mmHg, mean (SD) | 69.7 (21.4)  | 64.4 (27.0) | <0.001  | 59.2 (18.9)| <0.001  | 61.2 (21.0)    | <0.001  |
| pCO2 partial pressure, mmHg, mean (SD) | 66.6 (14-205) | 58.7 (24-205) | 0.43    | 33.7 (7.4)| 0.97    | 33.8 (68.1)    | 0.22    |
| Lactate mmol/L, mean (SD) | 33.9 (54.5) | 33.7 (7.4) | 33.0 (12-57) | 0.01 | 33.0 (12-70) | 0.001 | 1.5 (0.9) | <0.001 |
| Lactate mmol/L, median (range) | 1.2 (0.6) | 1.7 (1.1) | 1.4 (0.7-3.5) | 0.001 | 1.3 (0.5-7.8) | <0.001 |

Table 3: Laboratory findings predicting the events included in the primary outcomes (CPAP/NIV, ICU and death) in Covid-19 patients admitted to the Hospital of Crema between February 21st and March 13th, 2020, and followed up until March 19, 2020. Sums do not add up to the total because of some missing values. In bold, p values of clinically significant abnormal findings with Bonferroni adjusted significant p-values (i.e. p-values<0.017)