Differential diagnoses in COVID-19 pandemic: a retrospective descriptive study

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Contributions:

The presented idea of the study was conceived by E Rigamonti and P Gianella.

E Rigamonti wrote the manuscript with support from T Fusi-Schmidhauser and P Gianella.

G Argentieri contributed to figure preparation.

T Fusi-Schmidhauser supervised the project.

All authors read and approved the final version of the manuscript.

Disclosures about potential conflict of interests and further information

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We have no conflict of interest to declare.

This study was approved by the institutional ethics committee of Southern Switzerland as diagnostic quality review project.
Abstract
Since 02.2020, SARS-CoV-2 infection rapidly spread across Southern Switzerland. The available literature on differential diagnoses of COVID-19 is scarce. Our study aims to review differential diagnoses of SARS-CoV-2 infections in public hospitals in Southern Switzerland and to describe patients’ related outcome. Between 01.03.2020 and 15.04.2020, 344 patients had a chest CT-scan at admission, 210 of them were pathological. 172 patients had a positive nasopharyngeal swab for SARS-CoV-2 and 38 patients needed an additional diagnostic work-up and were included in this study. Among the selected patients, 8 patients underwent 2 PCR for SARS-CoV2, 18 of them 3 PCR. We observed 29 infective cases, 3 due to cardiovascular aetiologies, 2 due to COPD exacerbation, 1 due to cryptogenic organizing pneumonia, 3 not related to respiratory diseases. Our results highlight the importance of differential diagnosis in times of widespread occurrence of COVID-19, considering the similarity of symptoms and imaging appearance with other respiratory conditions.

Introduction
Since February 2020, the SARS-CoV-2 infection rapidly spread throughout Switzerland with a peak in confirmed cases between March 23 and 27th, 2020 (1-2). Southern Switzerland represented an epicentre for COVID-19 disease during this period, with 3327 reported cases, 350 fatalities and a cumulative prevalence of 94.2/10,000 cases at the end of June 2020 (3). Even in times of pandemic, it is of utmost importance to consider other differential diagnoses, since timely diagnosis and appropriate management may affect the outcome. During the 2009 influenza A (H1N1) pandemic, many bacterial co-infections and secondary infections occurred, resulting in substantial morbidity and mortality (4). Misdiagnosis was also a concern, due to availability bias, and treatable bacterial, viral or parasitic infections were mistakenly labelled as influenza A infections (5).

The available literature on differential diagnoses of SARS-CoV-2 infection is scarce. Single case
reports or series on infectious or non-infectious differential diagnoses, such as pulmonary contusion,
opportunistic infections, heart failure and drug-induced pneumonitis have been published (3, 6-9).
Furthermore, several papers were published in the early phases of the pandemics, where the
epidemiological situation was different (10, 11). Our study aims to review differential diagnoses of
SARS-CoV-2 infections in public hospitals in Southern Switzerland and to describe patients’ related
outcome.

Methods
Retrospective, descriptive study of patients who underwent a chest CT-scan with a pathological result
and were admitted to all EOC (Ente Ospedaliero Cantonale) hospitals in Southern Switzerland between
March 1st and April 15th 2020. Patients with suspicion of SARS-CoV-2 infection and at least one
negative RT-PCR for SARS-CoV-2 in nasopharyngeal specimens were included in the study. Case
definition for SARS-CoV-2 suspicion was defined by the institution as follows:
symptoms of acute respiratory disease, and/or fever without other explanations, and/or sudden loss of
sense of taste and/or smell, and/or acute delirium in the elderly or history of a close contact with a
confirmed COVID-19 case (at least 15 minutes at distance < 1.5 metres).

All clinical records of these patients were then reviewed, while evaluating the diagnostic work-up
necessary to establish a definite diagnosis. Demographic, clinical and laboratory data were coded and
collected on a duly created spreadsheet. Particular attention was given to collect and detail all
microbiological specimen (urines, faeces, induced sputum, broncho-alveolar lavage and serologies) in
patients with negative RT-PCR for SARS-Cov-2 in nasopharyngeal specimens, but with a pathological
CT-scan, in order to identify all patients with a COVID-19 disease.

Finally, we outlined the differential diagnoses that have been established by clinicians in charge of
these patients. The study was approved by the ethics committee of Southern Switzerland as a diagnostic
Results

A total of 344 patients had a chest CT-scan at admission and in 210 chest CT-scans pathological findings were described. 172 patients had a positive nasopharyngeal swab for SARS-CoV-2 and 38 patients needed an additional diagnostic work-up and were included in this study. Among the selected patients, 18 were males and 20 females, the average age of all included patients was 66 years. 8 patients underwent 2 PCR for SARS-CoV2, 18 of them 3 PCR. Among the 84 body fluids/specimens searched: in 50 cases, it was used nasopharyngeal swab, 16 PCR in induced sputum, 10 PCR in urines and faeces, 6 in broncho-alveolar lavage and finally 2 serologies. An overview of all demographic data is available in Table 1.

The majority of the alternative diagnoses to COVID-19 were infectious, with a predominance of bacterial pneumonia (22 patients, 57.9% of all cases), as depicted in Table 1. Other identified differential diagnoses included conditions with respiratory involvement, such as pulmonary embolism, acute heart failure and non-infectious COPD exacerbation. In 3 patients the established diagnosis was not respiratory-related (Table 1). The calculated mortality rate during hospital stay in all included patients was 10.8%. Among the discharged patients, 71.4 % of them could regain their home, while 28.6% of them were transferred to another hospital or rehabilitation clinic.

The following description of two clinical cases illustrates the challenges related with a timely and appropriate diagnosis and prompt treatment initiation during the COVID-19 pandemic in Southern Switzerland.

Case 1: bacterial infection due to Pseudomonas Aeruginosa

A 68 years old woman was admitted through the emergency room for dyspnoea and productive cough.
Her past medical history was remarkable for COPD stage 4D, severe malnutrition, anxiety-depression syndrome with opioid consumption and previous cutaneous *Pseudomonas Aeruginosa* infections resistant to carbapenems. The clinical examination showed an afebrile patient with low oxygen saturation at 86% in room air, the lung auscultation revealed diffuse wheezes.

The ECG was normal, the chest x-ray showed a bilateral accentuation of the lung parenchyma with small areas of infiltration in the lower left lobe. The laboratory exams highlighted a strong increase in inflammatory markers (CRP 178 mg/L) moderate lymphocytopenia (1.04 x10E9/L) and moderate increase in hepatic enzymes (ASAT 50 U/L, ALAT 71 U/L, alkaline phosphatase 177 U/L, gamma-GT 511 U/L). The nasopharyngeal swab PCR was negative for Influenza A and B, Respiratory Syncytial Virus and Sars-CoV-2. To complete the diagnostic work-up, we performed a RT-PCR for SARS-COV2 in a lower tract respiratory specimen (induced sputum), which was negative. An ultra-low-dose chest CT-scan showed multi-lobular infiltrates, which were suggestive for SARS-CoV-2 infection (Figure 1A-B) The clinical and radiological presentation was in favour of infectious exacerbation of COPD, and an empiric antibiotic therapy with amoxicillin/clavulanate and azithromycin was started. We assisted nonetheless to a progressive decline in respiratory conditions, and the patient deceased on the fourth day of hospitalisation. The induced sputum turned finally positive for extensive drug resistant *Pseudomonas Aeruginosa*.

**Case 2: bilateral pulmonary embolism**

A 48 years old woman with amyotrophic lateral sclerosis was admitted through the emergency room for worsening dyspnoea. The clinical examination showed a sub-febrile (T 37.5°C) patient with normal oxygen saturation in room air, the cardiopulmonary examination was unremarkable except for mildly reduced lung sounds in the right lower thorax.

The ECG showed a sinus rhythm at 95 bpm with s1q3 pattern, the laboratory exams highlighted a very
modest increase in C-reactive protein (7 mg/L) associated with mild lymphocytopenia (0.91 x10E9/L). We performed an ultra-low-dose chest CT-scan, which showed bilateral lower lobes infiltrates, with ground-glass areas compatible with interstitial viral pneumonia (Figure 2A). The nasopharyngeal swab PCR was negative for Influenza A and B, Respiratory Syncytial Virus and Sars-CoV-2. We completed the diagnostic work-up with a pulmonary angiographic CT-scan, which identified the presence of multiple pulmonary embolisms, the most remarkable at the right inferior lobe, with associated lung infarction (Figure 2B). An anticoagulation therapy was started in association with an antibiotic treatment with amoxicillin/clavulanate, the latter to treat a possible bacterial super-infection in the infarcted areas. The patient was discharged home in good general conditions after 5 days.

Discussion

Prompt recognition, isolation and rapid treatment initiation in suspected SARS-COV-2 cases are indispensable during this pandemic. However, lack of recognition of alternative differential diagnoses and/or co-infections may lead to delay in diagnosis and treatment. Our results highlight the importance of differential diagnosis even in times of widespread occurrence of COVID-19, considering the similarity of symptoms and imaging appearance with other respiratory and systemic conditions.

In our retrospective study, approximately 20% of hospitalised patients with clinical SARS-CoV-2 suspicion and pathological chest CT-scans, had an established alternative diagnosis. The reported fatality rate due to SARS-CoV-2 infection in Southern Switzerland (9.4%) and in the world (3.6%) (2). In our cohort, the case-fatality rate rises at 10.8%, suggesting that these patients seem to be vulnerable.

Our data suggest that establishing a diagnosis of SARS-CoV-2 only on clinical and radiological criteria may be a tricky diagnostic strategy. In fact, as above mentioned, one patient among five with respiratory symptoms and a pathological chest CT-scan will be diagnosed with an alternative condition
than COVID-19, such as other infectious and non-infectious diseases. The negativity of RT-PCR for SARS-Cov-2 in nasopharyngeal specimens should prompt to further investigate the presence of SARS-Cov-2 in other specimens, such as induced sputum, faeces and serum, while looking for differential diagnoses.

Study limitations are related to the retrospective design and the small sample size. Future studies of decision-making strategies to improve diagnostic accuracy of Sars-CoV-2 infections are warranted to help clinicians in daily practice.

Table 1: Demographics and microbiologic specimens of included patients

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients</td>
<td>38</td>
</tr>
<tr>
<td>Female (%)</td>
<td>20 (52.6)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>66.0 (16.6)</td>
</tr>
</tbody>
</table>

Number of SARS-CoV-2 RT-PCR

<table>
<thead>
<tr>
<th>Number of RT-PCR</th>
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<tbody>
<tr>
<td>One RT-PCR</td>
<td>11 (28.9%)</td>
</tr>
<tr>
<td>Two RT-PCR</td>
<td>8 (21.1%)</td>
</tr>
<tr>
<td>Three RT-PCR</td>
<td>19 (50.0%)</td>
</tr>
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</table>

Other specimens

<table>
<thead>
<tr>
<th>Specimen</th>
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<tbody>
<tr>
<td>Induced sputum</td>
<td>16 (19.0%)</td>
</tr>
<tr>
<td>Urines/faeces</td>
<td>10 (11.9%)</td>
</tr>
<tr>
<td>Broncho-alveolar lavage</td>
<td>6 (7.2%)</td>
</tr>
<tr>
<td>IgM/IgG serology</td>
<td>2 (2.4%)</td>
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Established diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Infectious</td>
<td>29 (76.3%)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>22 (57.9%)</td>
</tr>
<tr>
<td>Community-acquired</td>
<td>10</td>
</tr>
<tr>
<td>Streptococcus Pneumoniae</td>
<td>5</td>
</tr>
<tr>
<td>Ab ingestis pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Haemophilus Influenzae</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas Aeruginosa</td>
<td>1</td>
</tr>
<tr>
<td>Mycoplasma Pneumoniae</td>
<td>1</td>
</tr>
<tr>
<td>Legionella Pneumophila</td>
<td>1</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>5 (13.2%)</td>
</tr>
</tbody>
</table>
- Community-acquired = 3
- Adenovirus = 1
- Human Coronavirus OC43 = 1

**Fungal infection**
- Pneumocystis Jirovecii = 1

**Bacterial and viral coinfection**
- Haemophilus Influenzae and Adenovirus = 1

**Non-infectious**
- 9 (23.7%)
  - Cardiovascular
    - pulmonary embolism = 2
    - acute heart failure = 1
  - COPD exacerbation
    - Cryptogenic organizing pneumonia
  - Other
    - prosthesis-related infection = 1
    - left lower limb ischemia = 1
    - ischemic cerebral stroke = 1

1 (2.6%)

1 (2.6%)
Figure 1 (A) coronary and (B) sagittal chest CT-scan showing diffuse bilateral ground-glass opacities and multi-lobular infiltrates

Figure 2 (A) coronary chest CT-scan showing bilateral lower lobes infiltrates, with ground-glass areas compatible with interstitial viral pneumonia and (B) angio-CT-scan confirming the
presence of multiple pulmonary embolisms, the most remarkable at the right inferior lobe, with associated lung infarction

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