Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The impact of secondary infections in COVID-19 critically ill patients

Dear Editor,

We have read the systematic review and meta-analysis by Lansbury et al.[1], who highlighted the need for robust investigation to detect microbial co-infection and secondary infections in patients with COVID-19 to improved clinical knowledge and ameliorate the management of the patients, particularly for those admitted to the ICU. From early in the pandemic, such infections seemed to have played an important role, because they have been associated with a decreased survival, especially of severely ill patients[2]. Subsequent studies also reported the occurrence of co- or secondary infections in COVID-19 patients during hospitalization[3-5], often caused by multidrug-resistant (MDR) pathogens. Inflammatory biomarkers and microbiological surveillance were suggested to be important for the management of COVID-19 patients, allowing early detection of the indicators correlating with the presence of such infections and a negative outcome[6].

Here we report the clinical, laboratory and microbiological data of hospitalized COVID-19 patients admitted to the ICU of the S. Francesco Hospital of Nuoro (Sardinia, Italy) from March 2020 to May 2021, and evaluated the significance and the prognostic value of these parameters.

A total of 178 patients were enrolled in this study. Blood chemistry parameters (reflecting an inflammatory state and correlating with a secondary infection, and kidney and liver function) relative to three different time points were collected: 1) at the moment of the arrival to the emergency room, at the moment of admission to the infectious diseases ward or directly to the ICU; 2) between the admission day and the clinical outcome; and 3) before the transfer from the ICU to others wards or hospitals. Patients were grouped based on the different outcomes (Table 1). Microbiological data related to blood, bronchoaspirate, urine and intravascular devices specimens were collected every day and processed through diagnostic microbiological methods. Laboratory data were organized in matrices for both multivariate and univariate statistical analysis.

About 74% of the patients died while 26% were transferred to other hospital wards or other hospitals. Data were analyzed through a multivariate PLS approach, using as Y-variable the three different time points. The model showed a time-dependent distribution of the data based on the day of hospitalization. For the deceived patients, a significant increase in leukocytes, neutrophils, PCT, D-dimer, sodium and potassium and a decrease in hemoglobin and lymphocytes levels were observed. For the transferred patients, a significant increase in lymphocytes, sodium, platelets, and a significant decrease of neutrophils, hemoglobin, CRP, LDH, fibrinogen, creatinine and AST were found. From the microbiological point of view, 65% of the patients showed the presence of a secondary infection during the hospitalization in ICU and about 80% of these patients had a negative clinical outcome.

COVID-19, and possibly associated secondary infections, resulted in several laboratory alterations, with differences between the two groups. For the deceived patients, these alterations likely matched with the organism's failure to counteract infections and consequent organ damage, while, for the transferred patients, these changes were consistent with a probable clinical improvement.

A relevant aspect of this study regards secondary infections. From our analysis, it emerged that, of all the patients, 65% had positive cultures and, of these, 80% had a negative clinical outcome. Based on the data in the literature, the percentage of the COVID-19 patients with secondary infections is highly variable, ranging between 14% and 100%, also depending on the different inclusion criteria used[7]. Differences in the population, specimen source, and the isolated pathogens are likely responsible for the wide variations reported[8]. We observed a higher incidence of secondary infections compared to that reported in the paper of Lansbury et al.[1] and other studies[2-4,7-8]. This discrepancy may be because we included all the positive cultures, not distinguishing between contamination, colonization and infection. In both groups, a high percentage of Coagulase-Negative Staphylococci (CoNS) was isolated. However, an important aspect to be considered is the logistical conditions in which the healthcare personnel had to work in the considered period, in which there was a rapid and sudden increase in COVID-19 cases and ICU admissions. In fact, during these pandemic peaks, the ICU capacity of the hospital had to be increased by 300% to accommodate all patients requiring critical care.

Among the isolated species, *Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Candida* spp. and, above all, CoNS were mainly detected. These findings are in line with others published studies. During the hospitalization in ICU, *Klebsiella pneumoniae* isolates acquired resistance, such as the production of Extended-Spectrum β-Lactamases (ESBLs) and/or carbapenem-resistance, causing difficulties in the antibiotic treatment.

Based on our results, it seems clear that secondary infections have played a critical role in the negative outcome of the patients affected by severe COVID-19. Secondary infections may have acted as a reinforcing factor favouring the progression to a severe and fatal disease. Indeed, severe COVID-19 caused multiple damage[9], which may support rapid microbial growth. Morever, bacterial virulence factors can alter the immune responses, resulting in a rebound of SarS-CoV-2 infection and disease progression, leading to a higher mortality in critically ill patients[10].

The clinical presentation, the presence of co-morbidities, and the laboratory as well as the microbiology data can be valuable tools for identifying the most severe COVID-19 patients facing a poor prognosis. ICU represents a critical area for the management

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Table 1
Demographic data of the enrolled patients.

Database Covid-19	Patients	Age mean ± SD (Range)	F/M	Deceived[a](%)	Transferred[b](%)	Daysin ICU(Mean ± SD)
All	178	68.1 ± 11.3(22–88)	56/122	74	26	24 ± 15
Deceived	132	69.7 ± 9.5*(37–86)	42/90			17 ± 11
Transferred	46	63.2 ± 14.3(22–88)	14/32			31 ± 20

* = $p < 0.05$.
[a] Indicate the patients with a negative clinical outcome while hospitalised in this ICU.
[b] Indicate the patients that once became SARS-Cov2 negative were transferred to other wards or other hospitals, including other ICUs.

of patients with severe COVID-19. The lack of the implementation of the health resources may have been an indirect cause for the increased spread of infectious agents within the hospital, particularly in the ICU. The high frequency of isolation of pathogens associated with secondary infections may have also been caused by the fact that the most severe and critical ill COVID-19 patients in ICU underwent invasive procedures, which *per se* increase the risk of hospital-acquired infections and death. Monitoring the patients with serial microbiological examinations is crucial for choosing a proper antimicrobial treatment, avoid the development of resistance and the consequent spread of MDR microorganisms. This represents a complex global problem that cannot be ignored even the case of superimposing emergencies as that of the Sars-Cov2 pandemic

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Declaration of Competing Interest

The authors have no competing interests to declare.

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