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Short Communication

Increase of multidrug-resistant bacteria after the COVID-19 pandemic in a major teaching Hospital in Sicily (2018-2021)

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ABSTRACT

Introduction: The COVID-19 pandemic has further highlighted the continuing threat of antimicrobial resistance (AMR) to global health and economic development. In the last two decades, AMR has raised increasing concern, with an estimated 4.95 million deaths globally due to bacterial AMR in 2019 alone.

The aim of this study was to analyse the impact of the pandemic on the spread of multidrug-resistant organisms (MDROs) using data from the Hospital "P. Giaccone" in Palermo, comparing pre-pandemic and pandemic periods.

Methods: This observational study involved adult patients who were discharged from the hospital between 01 January 2018 and 31 December 2021. Hospital Discharge Cards were linked with microbiological laboratory reports to assess MDRO isolations. SARS-CoV-2 positivity during hospitalisation was evaluated using the National Institute of Health surveillance system.

Results: A total of 58 427 hospitalisations were evaluated in this study. Half the patients were aged over 65 years (N=26 984) and most admissions were in the medical area (N=31 716). During the hospitalisation period, there were 2681 patients (5%) with MDROs isolations, and 946 patients (2%) were positive for SARS-CoV-2. Multivariable analyses showed that during 2020 and 2021, there was a significantly increased risk of isolation of *Staphylococcus aureus, Acinetobacter baumannii*, and *Klebsiella pneumoniae*. Age, weight of the Diagnosis-Related Group (DRG), wards with higher intensity of care, and length-of-stay were associated with a higher risk of MDRO isolation.

Conclusion: This study provides new insights into the impact of the COVID-19 pandemic on MDRO isolation and has important implications for infection control and prevention efforts in healthcare facilities. Age, DRG-weight, and longer hospital stays further increased the risk of MDRO isolation. Thus, it is imperative to improve and follow hospital protocols to prevent healthcare-associated infections.

1. Introduction

The COVID-19 pandemic has further highlighted the continuing threat of antimicrobial resistance (AMR) to global health and economic development. The rise in multidrug-resistant infections during the pandemic led to significant morbidity, mortality, and economic loss [1]. In the last two decades, AMR has raised increasing concern, with an estimated 4.95 million deaths globally due to bacterial AMR in 2019 alone [2].

The COVID-19 pandemic not only caused a high number of infections and fatalities, but also directly affected the spread of AMR [3]. A recent review showed that 72.1% (1450/2010) of hospitalised patients with COVID-19 received antibiotics during their hospital stay, despite a relatively low rate (8%) of bacterial/fungal co- or secondary infections [4].

Inappropriate use of antimicrobials may have contributed to an increase in the number of multidrug-resistant organisms (MDROs), which pose a significant threat to global health [5]. In the context of these considerations, the objective of this study was to analyse

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the impact of the COVID-19 pandemic on the spread of specific MDROs using data from the University Hospital Policlinico "Paolo Giaccone" in Palermo. The study provided an opportunity to define the epidemiological trends and compare the spread of MDROs in the pre-pandemic and pandemic periods.

2. Methods

This was an observational, cross-sectional study, including patients aged at least 18 years who were discharged from the University Hospital Policlinico "Paolo Giaccone" in Palermo during the period 1 January 2018 to 31 December 2021. The 4-year observation period included 2 years (2018–2019) that preceded the emergence of SARS-CoV-2, and were free of COVID-related admissions (pre-pandemic period), and 2 years (2020-2021) that corresponded to the start of the SARS-CoV-2 pandemic (pandemic period), when the impact of COVID-19 on clinical care and organisational structure was more critical.

The year 2022 was excluded from the analysis as it was characterised by different organisational dynamics with respect to COVID-19 and data were not fully assessable.

Data were collected from the Hospital Discharge Form dataset and the ModuLab LIS laboratory management system, which recorded all hospital bacterial isolates with their antimicrobial susceptibility. The COVID-19 surveillance system of the Italian National Health System (ISS) was also used to evaluate the numbers of patients with COVID-19. Patients were classified as positive for COVID-19 if there was an overlap between the hospitalisation period and the positive period for SARS-CoV-2, with a tolerance of 3 days before or after the hospitalisation period. The social security number of the patients was used as a link between the three different data sources.

The protocol of the "Sistema Nazionale di Sorveglianza Sentinella dell'Antibiotico-Resistenza dell'Istituto Superiore di Sanità (AR-ISS)" - Protocol 2022, version March 17, 2022, developed by the Italian National Institute of Health was used to identify the MDROs of interest in this study. The AR-ISS protocol follows the proposal of the European surveillance EARS-Net to facilitate data transmission to the European Centre for Disease Prevention and Control (ECDC) and comparison at the European level [6].

The AR-ISS protocol includes information on eight bacterial species (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis, Enterococcus faecium*). The isolates included in the study belonged to this set of bacterial species and were isolated from selected biological samples (blood, cerebrospinal fluid) from patients included in the cohort. The protocol establishes a minimum set of antibiotics to be tested for each bacterial species, and the interpretative guidelines applied are those established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) [7]. Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories in accordance with the definition in the literature [8].

The evolution of the percentage of resistance to antibiotics was also assessed by comparing data from the different years for each microorganism. For all bacterial species, the percentage of resistance was calculated based on the antibiotics specified in the ISS protocol, except for *E. faecalis* and *E. faecium*, for which all tested antibiotics were considered.

To avoid duplicate values in individual patients who had multiple isolations of the same microorganism during the same hospitalisation episode, only the isolate with the worst resistance profile in terms of percentage was considered, according to the methodology described above. *S. pneumoniae* was excluded from individual microorganism assessments because of the very small number of isolations.

The contribution of different risk factors associated with the presence of MDROs was evaluated through logistic regression analysis. Specifically, for each MDRO, isolation (0=absence of isolation, 1=presence of isolation) was evaluated by independent variables, such as year of hospitalisation, sex, diagnosis-related group (DRG) weight, days of hospitalisation, age (18-45, 46-65, 66-74, over 74 years), DRG type, and SARS-CoV-2 positivity.

A DRG is a case-mix complexity system implemented to categorise patients with similar clinical diagnoses. The weight of the DRG provides a measure of the average resource consumption associated with hospitalisations pertaining to each DRG: the higher the weight, the higher the care burden of the corresponding case load [9].

2.1. Statistical Analysis

Qualitative and quantitative data were reported as frequencies and means (or medians, if appropriate), respectively. Normality of quantitative variables was tested using the Shapiro-Wilk test. Hospital wards of admission were stratified in tertiles based on their mean DRG weight, considered as a proxy of intensity of medical care. The chi-square trend test was used to analyse MDRO isolation trends and MDRO isolation association with intensity of care measured on the DRG weight of each ward. Logistic regression was used to evaluate risk factors associated with MDROs, considering variables like hospitalisation year, sex, DRG weight, hospitalisation days, age, DRG type, and SARS-CoV-2 positivity. Adjusted odds ratio (OR) and 95% confidence interval (95% CI) were calculated for each microorganism. Analyses were conducted using R (version 4.0.3), considering a P-value <0.05 as statistically significant.

3. Results

The antimicrobial susceptibility of 188 628 bacterial strains isolated from 58 427 hospitalisations from 2018 to 2021 was analysed in this study. As reported in Table 1, the highest number of admissions was recorded in 2019 (27.8%), with 15 952 hospitalisations, and the lowest was in 2020 (22.2%). The study population comprised 28 898 (49.7%) female and 29 529 (50.3%) male subjects, who were classified into four age groups (years): 18-45 (14 186; 24%), 46-64 (17 798; 30.1%), 65-74 (12 773; 21.6%), and over 74 (14 470; 24.4%). The median DRG weight was 1.14 (interquartile range: 0.77–1.36), and the majority of hospital admissions were in the medical area (32 319; 54.6%). Of all hospitalisations, 950 patients (1.6%) tested positive for SARS-CoV-2 during their hospital stay. The most commonly isolated MDROs were *K. pneumoniae* (1274 isolations) and *E. coli* (952 isolations).

The trend analysis of MDRO isolations showed that there was a statistically significant increase in the incidence of all investigated microorganisms during the COVID-19 pandemic period. Multivariable logistic regression analyses (Figure 1) showed that *S. aureus* isolation increased in 2020 (OR=1.43; P=0.02) and in 2021 (OR=1.39; P=0.04), *A. baumannii* increased in 2020 (OR=1.45; P=0.003) and in 2021 (OR=1.38; P=0.010), and *K. pneumoniae* increased in 2020 (OR=1.37; $P<0.001$) and in 2021 (OR=2.00; $P<0.001$). Male subjects were less susceptible to MDR *E, coli* infections (OR:0.86; P=0.03).

When analysing the presence of more than one MDR isolate from the same patient, the data showed an increase in multiple MDRO infections during 2020 (OR=1.27; $P<0.001$) and an even greater increase during 2021 (OR=1.43; $P<0.001$). The increase in DRG weight was associated with a 39% increase in the risk of MDR isolates (OR=1.39; $P<0.001$), whereas the surgical DRG type was

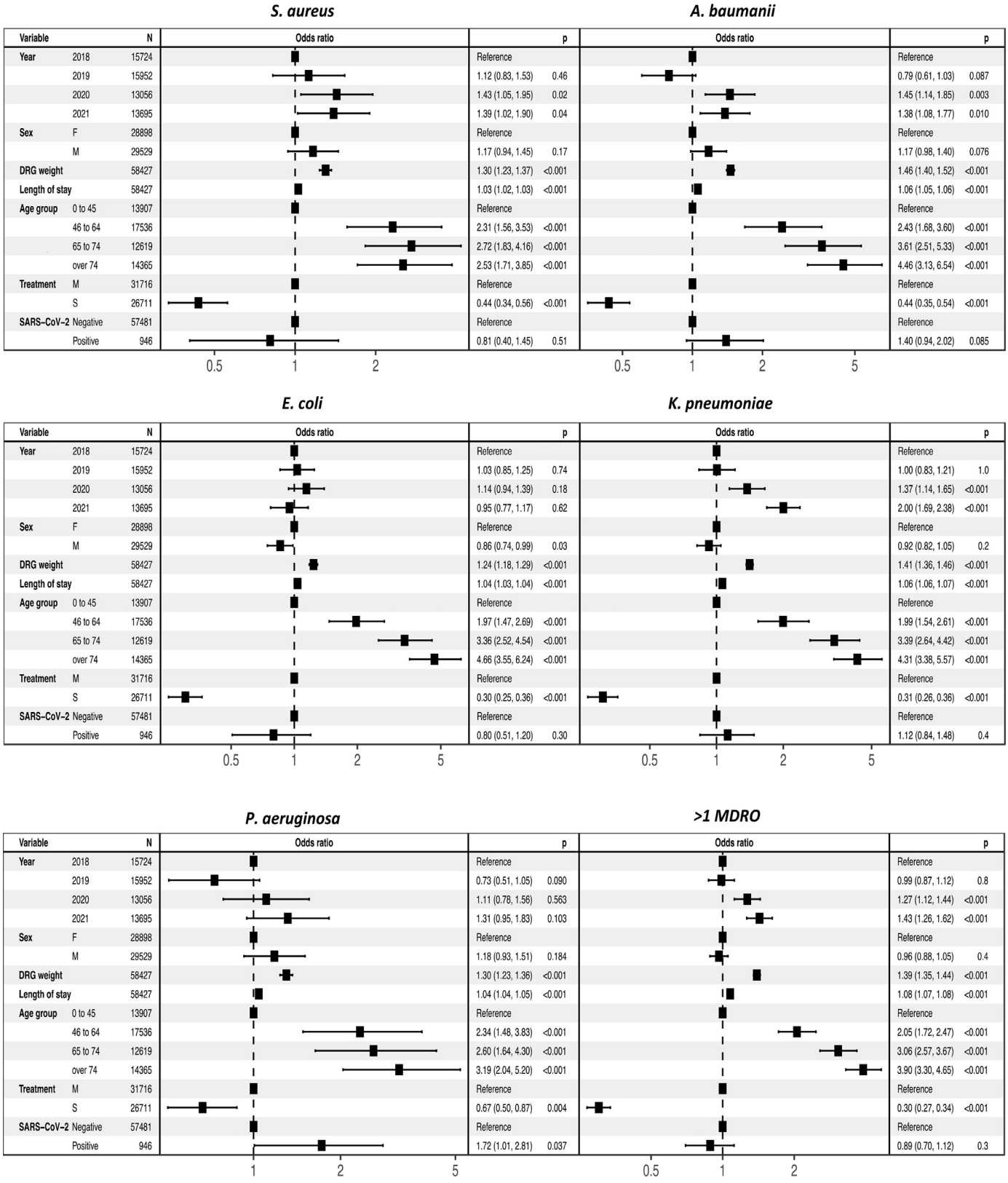

Figure 1. Forest plots showing the odds ratios (OR) and 95% confidence interval (CI) for MDR isolates.

found to be a significant protective factor (OR=0.3; $P<0.001$). Hospital length of stay was a risk factor for MDRO isolates (OR=1.08; $P<0.001$). The most significant risk factor was found to be age, with a significant increase in the risk of MDRO isolates in the age groups 65-74 (OR=3.06; $P<0.001$) and over 74 (OR:3.90; $P<0.001$) years. Overall, the analyses showed that SARS-CoV-2 positivity did not significantly increase the risk of MDRO infections. Moreover, analysing the risk of MDRO isolation according to intensity of care of admission wards showed that this risk increased with intensity of medical care, with 2%, 6.7% and 5%, respectively, in low,

Table 1
Main clinical and demographic characteristics of the hospitalised patients, and characteristics of MDRO isolates during the study period, including Diagnosis-Related Groups (DRGs) features.

	N	*%*
Total	59 227	*100%*
Year		
2018	15 791	26.7%
2019	16 437	27.8%
2020	13 135	22.2%
2021	13 864	23.4%
Sex		
Male	29 781	50.3%
Female	29 446	49.7%
Age (in years)		
18-45	14 186	24%
46-64	17 798	30.1%
65-74	12 773	21.6%
over 74	14 470	24.4%
MDRO		
S. aureus	359	0.6%
A. baumanii	637	1.1%
E. coli	952	1.6%
K. pneumoniae	1274	2.2%
P. aeruginosa	306	0.5%
>1 MDRO Isolate	2681	4.5%
DRG Weight		
less than 1.00	27 708	46.8%
between 1.00-2.00	23 073	39%
between 2.00-3.00	4487	7.6%
more than 3.00	3959	6.7%
DRG Type		
Surgical	26 908	45.4%
Medical	32 319	54.6%
SARS-CoV-2 Test		
Negative	58 277	98.4%
Positive	950	1.6%

medium and high intensity of care ($P<0.001$) (data not shown in table).

4. Discussion

The impact of the COVID-19 pandemic on global antimicrobial resistance is yet to be fully understood and is likely to vary among different populations and disease hotspots. Certain changes in human behaviour and healthcare practices brought about by the pandemic, such as improved infection control measures and increased hygiene, may have reduced the impact of COVID-19-related antibiotic use on AMR [10]. On the other hand, the disproportionate use of antibiotics in COVID-19 patients could have exacerbated the issue of AMR in areas already highly affected, such as Italy and the United States [11,12].

In this context, a first point of interest of the current study is the geographical setting, as Italy is one of the European countries most heavily impacted by antibiotic resistance. The current study findings align with previous research showing that patients positive for COVID-19 are not more prone to develop MDRO infections. Although patients with COVID-19 who were hospitalised for pneumonia were likely to have received excessive amounts of antibiotics, they were also possibly overprotected against other infections during the pandemic period because of a broader and more appropriate use of standard precautions, such as using gloves or handwashing [13,14].

Conversely, the current study showed that during the pandemic period, patients were more likely to be colonised by MDRO (OR=1.27 in 2020 and OR=1.43 in 2021), indicating that although COVID-19 patients might not be significantly affected, the pandemic might have disrupted antimicrobial stewardship (AMS) activities. The negative impact of COVID-19 on AMS can be attributed to several factors. The fight against the virus consumed most of the healthcare system resources, leading to a decrease in funding for hospitals and other non-primary health services. In addition, various COVID-19 management strategies, such as the prioritisation of healthcare worker safety and post-exposure prophylaxis shortages, coupled to overcrowded hospitals and low healthcare worker-to-patient ratios, have contributed to disruptions in antimicrobial surveillance and an increase in antimicrobial use, favouring the spread of MDRO [15,16].

Another important finding of the current study was the strong link between length of hospital stay and risk of MDRO infections, which is a known link and has been reported in the literature [17]. However, length of stay in a hospital ward can be both a cause and a consequence of MDRO infections. This interplay between length of stay and MDRO infections creates a vicious cycle: MDRO infections increase the length of hospital stay, which in turn increases the risk of further MDRO infections [18,19].

According to the current study results, the intensity of hospitalisation care, measured by the proxy of the Diagnosis-DRG, is unavoidably linked to an increased risk of contracting MDRO infections. In fact, DRG weight is determined by several factors, including the severity of the patient's illness or injury, the type of treatments and procedures required, and the length of hospital stay, which is a known risk factor for MDRO infections. Medical procedures and the placement of devices, such as catheters and intravenous lines, increase the risk of infection as they create more opportunities for bacteria to enter the body [20]. However, the current study findings also indicate a protective role of the surgical DRG type, which might be due to the shorter hospital stays in surgery wards.

The link between the intensity of medical care and the prevalence of MDRO infections is reinforced by Wang et al. [21], who highlight a pronounced relationship between higher levels of care intensity and the incidence of MDRO infections. This pattern is consistent with the current study data showing that patients with higher DRG weight categories - and consequently more complex care needs - exhibit an increased risk of these infections. There were no comprehensive data regarding MDRO infections among healthcare staff in the current study; therefore, connections to specific wards cannot be made. A further limitation of the current study is the lack of complete and representative data on the use of catheters and other medical instruments.

Age was the most significant risk factor for MDRO infections in the current study. This is not surprising as MDRO infections are common in older people, particularly in specialised healthcare facilities, such as nursing homes, where they can reach a 50% prevalence [22].

There are no data in the literature to support a possible association between male sex and increased risk of *E. coli* MDRO isolation indicated in the current study; therefore, this association may be due to chance.

One of the main limitations of the current study on antibiotic resistance was that data were from only one hospital; therefore, the results may not be generalisable to other settings. Furthermore, the accuracy of the data may be impacted by the quality of infection control measures and the completeness of the hospital infection control records.

Future research should focus on developing more comprehensive and standardised methods for defining, collecting, and analysing data on antibiotic resistance, to better understand the underlying causes and mechanisms of this complex problem.

Also important is the development of more effective strategies for fighting antibiotic resistance, including the development of novel antibiotics and alternative therapies, as well as the implementation of AMS programmes in hospitals and other healthcare settings.

5. Conclusion

The current study provides new insights into the impact of the COVID-19 pandemic on MDRO isolation and has important implications for infection control and prevention efforts in healthcare facilities. Although SARS-CoV-2 infection was not a risk factor for MDRO isolation, the pandemic has had a strong negative impact on the matter. Age, DRG-weight, and longer hospital stay further increase the risk of MDRO isolation.

The results of this research contribute to a greater understanding of the issue of MDRO infections and will ideally inform future efforts to address this growing public health challenge.

CRediT authorship contribution statement

Emanuele Amodio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Stefano Pizzo:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing, Data curation, Writing – original draft. **Giuseppe Vella:** Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Valerio De Francisci:** Writing – original draft, Writing – review & editing, Investigation, Formal analysis. **Salvatore Antonino Distefano:** Data curation, Investigation, Methodology, Writing – review & editing. **Eliana Giambelluca:** Data curation, Validation. **Domenico Graceffa:** Data curation, Investigation, Methodology, Writing – review & editing. **Maria Gabriella Verso:** Data curation, Investigation, Methodology, Writing – review & editing. **Ettore Piro:** Data curation, Investigation, Methodology, Writing – review & editing. **Mario Giuffrè:** Data curation, Investigation, Methodology, Writing – review & editing. **Giovanni Maurizio Giammanco:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing. **Giuseppe Calamusa:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing.

Declarations

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Competing Interests: There are no conflicts of interest to declare

Ethical Approval: The study was approved by the Ethical Committee of the A.O.U.P. “P. Giaccone” on June 24th, 2020, Protocol Number CEP/2020/06).

Sequence Information: Not applicable

Availability of data and material (data transparency)

Data available on request due to privacy/ethical restrictions.

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