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ORIGINAL RESEARCH

K-Means Clustering Identifies Diverse Clinical Phenotypes in COVID-19 Patients: Implications for Mortality Risks and Remdesivir Impact

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ABSTRACT

Introduction: The impact of remdesivir on mortality in patients with COVID-19 is still controversial. We aimed to identify clinical phenotype clusters of COVID-19 hospitalized patients with highest benefit from remdesivir use and validate these findings in an external cohort.

Methods: We included consecutive patients hospitalized between February 2020 and February 2021 for COVID-19. The derivation cohort comprised subjects admitted to Hospital Clinic of Barcelona. The validation cohort included patients from Hospital Universitari Mutua de Terrassa (Terrassa) and Hospital Universitari La Fe (Valencia), all tertiary centers in Spain. We employed K-means clustering to group patients according to reverse transcription polymerase chain reaction (rRT-PCR) cycle threshold (Ct) values and lymphocyte counts at diagnosis, and pre-test symptom duration. The impact of remdesivir on 60-day mortality in each cluster was assessed.

Carolina Garcia-Vidal, Christian Teijón-Lumbreras, and Tommaso Francesco Aiello contributed equally to this manuscript.

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Results: A total of 1160 patients (median age 66, interquartile range (IQR) 55–78) were included. We identified five clusters, with mortality rates ranging from 0 to 36.7%. Highest mortality rate was observed in the cluster including patients with shorter pre-test symptom duration, lower lymphocyte counts, and lower Ct values at diagnosis. The absence of remdesivir administration was associated with worse outcome in the high-mortality cluster (10.5% vs. 36.7%; $p<0.001$), comprising subjects with higher viral loads. These results were validated in an external multicenter cohort of 981 patients.

Conclusions: Patients with COVID-19 exhibit varying mortality rates across different clinical phenotypes. K-means clustering aids in identifying patients who derive the greatest mortality benefit from remdesivir use.

Keywords: COVID-19; Antiviral agents; Clustering; Artificial intelligence

Key Summary Points

Patients with COVID-19 show varying mortality rates among different clinical phenotypes.
Multiple randomized studies have evaluated the efficacy of different antiviral strategies but the results are disparate and difficult to interpret.
Clustering K-means method identified different clinical phenotype of patients with COVID-19 and varying risk of mortality and response to remdesivir.
Higher mortality occurred in patients with lower rRT-PCR Ct at COVID-19 diagnosis.
For those patients, the absence of remdesivir is associated with worse outcomes.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus responsible for COVID-19. This virus has caused one of the most significant pandemics of this century, accounting for more than seven million deaths [1]. SARS-CoV-2 remains a global health threat to date, and multiple questions about treating and managing patients infected with the virus remain unresolved.

Understanding the impact on mortality associated with the use or not of antivirals in different phenotypes of hospitalized patients with COVID-19 is currently one of the most significant challenges. Remdesivir was the first antiviral treatment approved for this infection. Multiple randomized studies were conducted in record time to test the utility of this drug. However, the different clinical trials described disparate results. Whilst some analyses showed that remdesivir improved the outcomes of patients with COVID-19 [2–6], other studies doubted this benefit [7–10]. A plausible explanation may be that clinical phenotypes differ for patients with COVID-19, and the impact of different treatments could be more or less important [11–13]. As a result of these controversial findings [14], despite the benefits of remdesivir in different outcomes being clear for some physicians, other colleagues have expressed their concern about the usefulness of this antiviral in terms of mortality. Consequently, during various pandemic waves certain medical societies did not advocate for or against remdesivir administration in their COVID-19 treatment guidelines [15, 16].

Our hypothesis is that cluster analysis using relatively large amounts of data can help to identify groups of patients who share similar viral status. Those with higher viral load would have worse outcomes, as previously reported [12, 17–20], and will be those who more benefit from the remdesivir administration in terms of reduced mortality. We use non-supervised clustering techniques (K-means) to identify clinical phenotypes of patients with different viral involvement and define the impact of remdesivir on mortality in each clinical cluster. We

validate these results in a separate multicenter cohort.

METHODS

Study Design and Population

The derivation cohort comprised patients admitted to the Hospital Clinic of Barcelona, a 700-bed university center providing medical, surgical, and intensive care for a population of 500,000 adults. We included all consecutive patients hospitalized for SARS-CoV-2 infection between February 2020 and February 2021 and who met all of these criteria: (1) hospital admission for more than 48 h; (2) real-time reverse transcription polymerase chain reaction (rRT-PCR) testing performed on nasal and oropharyngeal swab specimens confirming COVID-19 diagnoses and providing information on cycle threshold (Ct) values; (3) recorded data from pre-test duration of symptoms; (4) at least one determination of lymphocytes count within the first 48 h of hospital admission. Concerning remdesivir administration, patients eligible for antiviral treatment were those with pneumonia requiring supplemental oxygen, according to the recommendation of the European Medicines Agency (EMA) and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). The recommended dose was 200 mg on the first day administered by intravenous infusion, followed by a daily dose of 100 mg by intravenous infusion, with the total treatment duration being 5 days. The validation cohort included patients with identical inclusion criteria from Hospital Universitari Mutua de Terrassa (Terrassa) and Hospital Universitario La Fe (Valencia), both tertiary centers in Spain. Only the information necessary to perform the clustering algorithm and the evaluation of the efficacy of remdesivir was obtained.

High-quality anonymized data on demographic characteristics, clinical signs, laboratory tests, microbiologic results, treatments, and outcomes were collected directly from electronic health records (EHR) as described elsewhere [21]. The quality of data was assessed by a multidisciplinary team including physicians and data scientists. The methodology of this study strictly adheres to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) standards [22].

The Institutional Ethics Committee of the Hospital Clinic of Barcelona approved the study and, as a result of the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

Statistics

Categorical variables were described using the absolute number and percentage, whilst continuous variables were presented using the median and interquartile range (IQR). Categorical variables were compared with either a chi-squared (χ^2) test or Fisher's exact test when appropriate, and quantitative variables with the Mann–Whitney *U* test. Statistical significance was defined as $P<0.05$. We created different clusters of patient phenotypes using three variables directly related to the virus load: Ct of rRT-PCR and total lymphocyte count at COVID-19 diagnosis, and data from pre-test duration of symptoms. The clustering algorithm selected was K-means. This is a multidimensional type of learning methodology capable of integrating multiple characteristics of patients to create various clusters with similarities. With this technique, cluster centers are initially generated pseudo-randomly. After that, each patient is integrated into the cluster with the nearest cluster center. The cluster centers are then recomputed with the means of the selected variables belonging to that cluster. Following that, patients are reclassified with the new cluster centers. This process is repeated until convergence, and patients stop switching clusters and cluster centers stop moving. To determine the optimal number of cluster centers, we used the elbow method. Afterwards, the impact of the use of remdesivir on 60-day mortality of patients included in each cluster was analyzed using a χ^2 test. The supplementary material contains a more detailed explanation of the K-means clustering method and the elbow method. The algorithm was validated in a multicenter external cohort. The threshold for statistical significance

was defined as a two-tailed $p<0.05$. Analyses were performed with Python, version 3.10.8, R-software, version 4.2.2 and Microsoft SPSS-PC+, version 22.0 (SPSS, Chicago, IL, USA).

RESULTS

During the study period, we assessed 1160 consecutive adults in the derivation cohort who met the inclusion criteria. Table 1 summarizes the main epidemiologic and clinical characteristics of these patients. The median age was 66 (IQR 55–78) years, and 59.4% of the cohort were male. The median pre-test duration of symptoms was 6 days (3–8); the median Ct of rRT-PCR at COVID-19 diagnosis was 26.5 (IQR 22–30.6); and the median lymphocyte count at onset was 0.8×10^9/L (IQR 0.6–1.1). Table 1a in the supplementary material shows patients' baseline characteristics in each cluster. The overall 60-day mortality was 14.22%. As detailed in Fig. 1, higher mortality was observed in patients with the shortest days from pre-test duration of symptoms, and lower lymphocyte count and Ct value of rRT-PCR at COVID-19 diagnosis.

Clustering of Patients According to Viral Phenotype

Using data on Ct value of rRT-PCR, total lymphocyte counts at COVID-19 diagnosis, and pre-test duration of symptoms, we created groups of similar patients according to viral phenotype by the K-means technique. The elbow method determined the best maximum at five clusters. Figure 2 and video 1 in the supplementary material show the distribution in three dimensions of patients in the five K-means clinical clusters according to their viral phenotype measured by pre-test duration of symptoms, lymphocyte count, and Ct value of rRT-PCR at COVID-19 diagnosis.

Table 2 details the main characteristics of patients selected in each cluster. Rates for 60-day mortality per cluster were 2%, 11%, 8.2%, 10.4%, and 29.7%, respectively.

Impact of Remdesivir on Mortality for Each Patient Cluster Per Viral Phenotype in the Derivation Cohort and External Algorithm Validation

Significantly higher 60-day mortality was documented in those patients not receiving remdesivir in cluster 5 (10.5% vs 36.7%; $p<0.001$). This cluster included 286 (24.7%) patients from the derivation cohort. These patients had the highest mortality rates, lowest lymphocyte count, and the shortest median days of pre-test duration of symptoms, mainly associated with lower Ct of rRT-PCR at COVID-19 diagnosis. Figure 3 details the 60-day mortality in each cluster for those patients receiving remdesivir compared with those patients who did not receive the drug in the derivation cohort. The utilization of remdesivir was observed across all clusters. In cluster 5, it is noted that mortality is particularly high in the absence of remdesivir.

An external validation cohort was used to verify the utility of the algorithm (Table 2). A total of 902 patients included in the validation cohort were assigned to a cluster, using the cluster centers computed via K-means, with the initial cohort (patients were assigned to the cluster whose center was nearest to them). Results were consistent, and patients not receiving remdesivir in cluster 5 had significantly higher 60-day mortality (11.1% vs 25.6%; $p<0.044$).

DISCUSSION

Our study undertook an innovative approach using a clustering algorithm to identify different clinical phenotypes of patients hospitalized with COVID-19 with varying infection viral load to assess the role of remdesivir use in terms of mortality. We documented significant differences in this important outcome amongst clusters. These results are of great importance as they confirm that those patients with higher viral load benefitted more, even in terms of reduced mortality, from remdesivir use. Moreover, our results highlight the potential use of computers, especially

Table 1 Main epidemiologic and clinical characteristics of patients in the derivation cohort

	Patients (*N* = 1160)
Patient characteristics	
Age-median (IQR), in years	66 (55–78)
Sex male, *n* (%)	688 (59.4)
Comorbidities, *n* (%)	
Hypertension	517 (44.6)
Chronic heart disease	291 (25.1)
Chronic lung disease	276 (23.8)
Diabetes mellitus	221 (19.0)
Solid neoplasm	178 (15.3)
Hematological malignancies	78 (6.7)
Chronic liver diseases	71 (6.1)
Vital signs at admission, median (IQR)	
Temperature (°C)	37.3 (36.6–38)
Respiratory rate (rpm)	20 (18–24)
Oxygen saturation (%)	95 (93–97)
Laboratory values at admission, median (IQR)	
Ferritin (ng/mL)	580 (274–1088)
CRP (mg/dL)	7.9 (3.8–14.2)
D-dimer (ng/mL)	700 (400–1300)
LDH (U/L)	315 (251–400)
Lymphocyte count ($\times 10^9$/L)	0.8 (0.6–1.1)
Median (IQR) cycle threshold (Ct) at COVID-19 diagnosis	26.5 (22.0–30.1)
Ct ≤ 20, *n* (%)	173 (14.9)
Ct between 21 and 25, *n* (%)	297 (25.6)
Ct > 25, *n* (%)	690 (59.5)
Median (IQR) days of pre-test duration of symptoms	6 (3–8)
Intensive care unit admission, *n* (%)	244 (21.0)
60-day mortality, *n* (%)	165 (14.2)

CRP C-reactive protein, *LDH* lactate dehydrogenase

with their ability to cluster patients, to improve the decision-making process in relation to antiviral use.

Remdesivir received definitive approval by health authorities as COVID-19 treatment in October 2020. However, two trials assessing

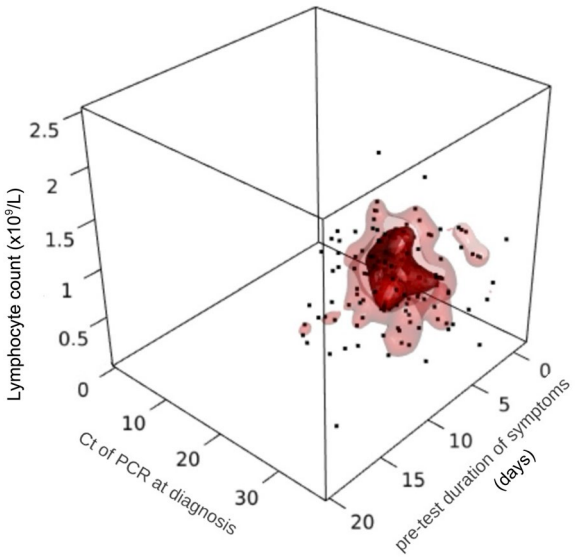

Fig. 1 60-day mortality density on 1160 consecutive patients hospitalized with COVID-19 in the derivation cohort depending on the pre-test symptom duration (days), Ct of rRT-PCR, and lymphocyte count ($x10^9$/L) at COVID-19 diagnosis. Deceased patients are represented by dots. In areas with a high density of dots, bubbles with different intensities are generated to optimize the visualization. Lymphocyte count is expressed as cells/mm^3; duration of symptoms is expressed in days. Higher mortality was observed in those patients with lower pre-test duration of symptoms, Ct less than 25, and a lower number of lymphocytes at diagnosis

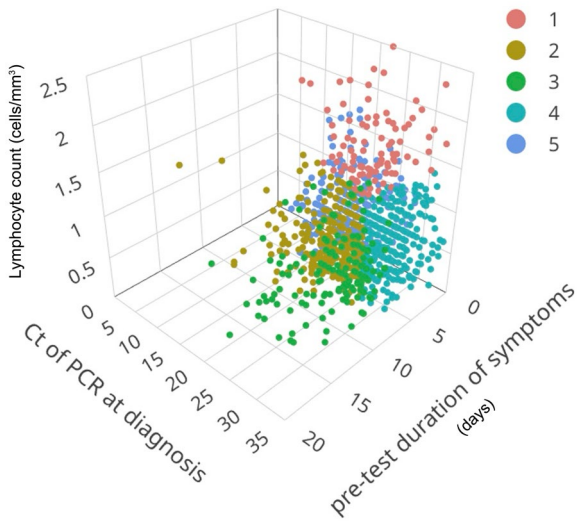

Fig. 2 Distribution of K-means clusters of patients according to their clinical phenotype in three dimensions. Clusters are represented by dots of the same colors. Lymphocyte count is expressed as cells/mm^3; duration of symptoms is expressed in days

the impact of remdesivir use on outcomes in patients with COVID-19 did not find any benefits in clinical improvement or mortality. Amongst the 237 randomized patients in the first study, the median time from symptom onset to remdesivir use was 11 days; 19% of patients had undetectable viral RNA in rRT-PCR at trial inclusion; and 32% of patients had a lymphocyte count of more than 1000 when remdesivir was started [7]. The second study had no data reporting patient characteristics in relation to any of these variables [8]. Data on Ct values in rRT-PCR at COVID-19 diagnosis were lacking in both studies.

Conversely, other trials demonstrated clinical benefits from the use of remdesivir [2, 5, 7, 8, 11, 12]. This benefit was more pronounced in patients who had shorter pre-admission duration of symptoms. Data on lymphocyte count or Ct in rRT-PCR at diagnosis were not reported.

In our study the clustering K-means method optimally classifies patients depending on the viral load and a worse response to viral infection—as defined by lower Ct of rRT-PCR and lymphocyte count at COVID-19 diagnosis and shorter pre-test duration of symptoms—and it helps to draw a clear clinical picture of different mortality rates. These findings are consistent with those previously reported in clinical studies [17, 23–25] and strengthen the link between viral load and mortality. Furthermore, these observations reinforce the idea that administering early antiviral treatment should be important in improving mortality of specific patients hospitalized with COVID-19.

Studies on the impact of new antiviral strategies in patients with COVID-19 have been recently conducted. All these therapeutic approaches have mainly been tested on patients within the initial days following a COVID-19 diagnosis; results are encouraging [26–30]. Our study shows that controversial results may be explained by the heterogeneity of patient characteristics at inclusion. Thus, researchers

Table 2 Main characteristics of five clusters of patients selected by K-means, according to their viral phenotype in the derivation and validation cohorts

K-means cluster	Median Ct (IQR)	Median days of pre-test duration of symptoms (IQR)	Median lymphocyte count (IQR) ($\times 10^9$/L)	60-day mortality (%)	60-day mortality/pts receiving remdesivir (%)	60-day mortality/pts who did not receive remdesivir (%)	*p* value
Cluster 1							
Derivation cohort *n* = 100	26 (23–30)	5 (3–7)	1.7 (1.5–2)	2	0	2.4	0.54
Validation cohort *n* = 167	25 (22–29)	6 (4–7)	1.8 (1.6–2.2)	6.6	0	7.2	0.28
Cluster 2							
Derivation cohort *n* = 273	24 (22–26)	8 (7–9)	0.8 (0.6–1)	11	0	11.3	0.35
Validation cohort *n* = 292	21 (18–25)	8 (7–9)	0.9 (0.7–1.1)	7.2	3.2	7.7	0.37
Cluster 3							
Derivation cohort *n* = 183	31 (29–34)	11 (10–13)	0.8 (0.6–1.1)	8.2	NA	8.2	N/A
Validation cohort *n* = 121	30 (26–32)	12 (10–14)	1.1 (0.8–1.5)	7.4	0	7.5	N/A
Cluster 4							
Derivation cohort *n* = 318	31 (29–33)	5 (4–7)	0.8 (0.6–1)	10.4	2.9	11.3	0.13
Validation cohort *n* = 156	31 (29–33)	5 (3–7)	0.9 (0.7–1.2)	12.8	13.8	12.6	0.86
Cluster 5							
Derivation cohort *n* = 286	21 (17–23)	3 (1–4)	0.7 (0.5–0.9)	29.7	10.5	36.7	< 0.001

Table 2 continued

K-means cluster	Median Ct (IQR)	Median days of pre-test duration of symptoms (IQR)	Median lymphocyte count (IQR) ($\times 10^9$/L)	60-day mortality (%)	60-day mortality/pts receiving remdesivir (%)	60-day mortality/pts who did not receive remdesivir (%)	*p* value
Validation cohort $n = 166$	19 (16–22)	3 (2–4)	0.8 (0.6–1.0)	21.7	11.1	25.6	0.044

N/A: not applicable

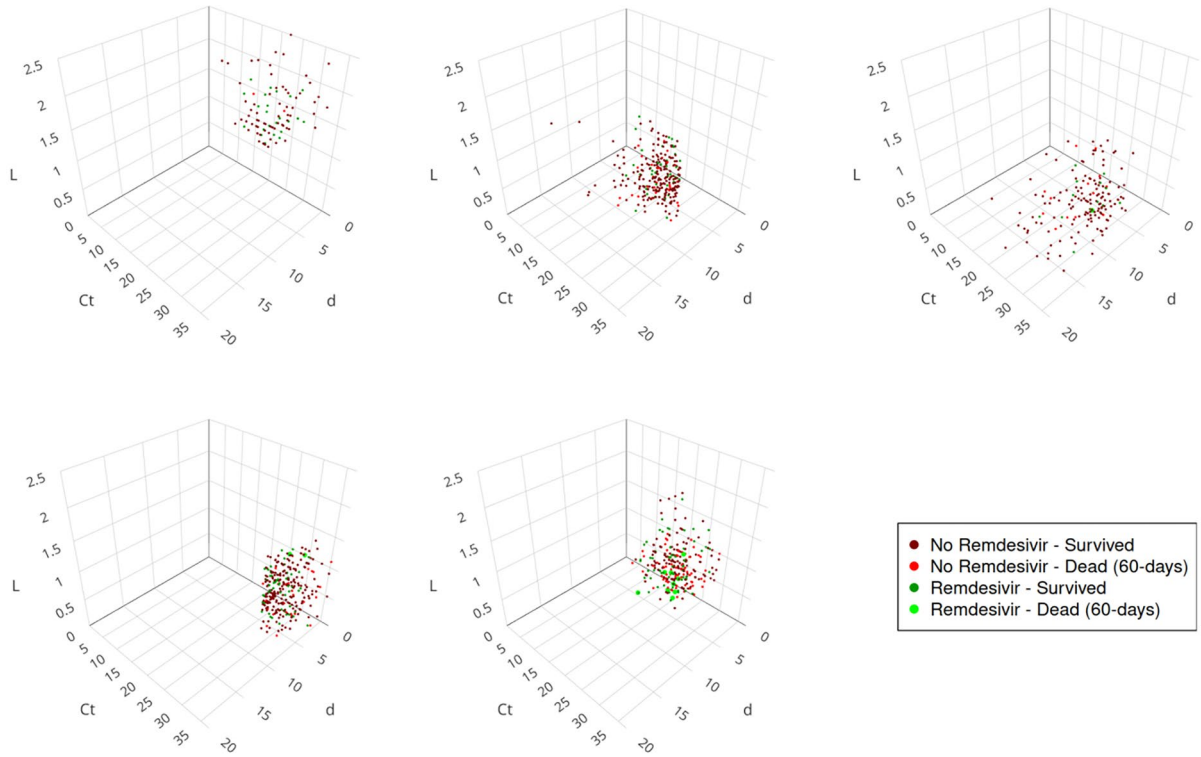

Fig. 3 60-day mortality in patients receiving remdesivir and those who did not receive remdesivir by clusters in the derivation cohort. Clusters 1 to 5 are consecutively represented in each three-dimensional diagram (clockwise from top-left). Dots represent patients, with different colors identifying remdesivir treatment and mortality outcome. "L" stands for lymphocyte count, expressed as cells/mm^3; "d" stands for duration of symptoms in days; Ct stands for Ct of rRT-PCR at diagnosis

evaluating the impact of treatments on COVID-19 prognosis should describe those phenotypes more precisely to better explain why those treatments are beneficial in some cases while not in others. In this context, providing clustering methods that assist physicians with objectively classifying patients and/or analyzing a large number of variables will be breakthrough in medicine. This methodology makes it possible to have objective, reproducible classifications, available with a small, 24/7 computer support tool for all physicians, irrespective of

their expertise. The use of clustering algorithms in medical research remains scarce, and some authors have expressed concern about the black box that some algorithms or clustering performed by a computer may represent [21]. However, studies such as ours, in which computers perform clustering of patients based on variables determined by our team, and confirm results in an external validation cohort, strengthen our confidence in these techniques. To our knowledge, this is the first study that demonstrated the impact of a specific antiviral treatment in patients classified with an unsupervised clustering algorithm and confirmed the results using an external validation cohort.

The main limitations of our study include the following. First, we did not have any information on the specific SARS-CoV-2 variants in our patients. The most frequent circulating variants throughout the study period included SARS-CoV-2 Wuhan-1 and B.1.1.7 (alpha). Further studies are necessary to analyze whether our results could be extrapolated to other new viral variants, as susceptibility of SARS-CoV-2 to the antiviral may potentially change according to the appearance of mutations in the antiviral target. Second, we have no information on patients' vaccine status. As a result of the study period, most patients in this cohort were not vaccinated. The results in the vaccinated population might be different. Indeed, in our study, viral load and the potential host response to SARS-CoV-2 were analyzed directly by Ct of rRT-PCR and indirectly by lymphocyte count and pre-test duration of symptoms. It would be plausible to consider modifications in these variables due to vaccination and SARS-CoV-2 new variants' susceptibility to current vaccination regimen. That stated, there is a need for future studies to investigate the impact of these values, particularly among vaccinated patients, on the relationship between prognosis and the use of remdesivir. Finally, we focus on mortality, and other potential benefits of remdesivir in outcomes are not analyzed. Another important aspect to be further investigated in the future is the evolution of the clinical phenotype of COVID-19 during pandemic waves. Examining the evolution of viral phenotypes throughout the pandemic, as well as their relationship with secondary inflammation due to COVID-19, would be of interest. This knowledge could guide us in understanding the importance of antiviral strategies compared to other COVID-19 treatments, with a more focused approach on controlling inflammation.

CONCLUSION

Our clustering algorithm identified that among hospitalized patients with COVID-19, those with lower Ct value of rRT-PCR and lymphocyte count at diagnosis, and shorter pre-test duration of symptoms had higher mortality. For those patients, the absence of remdesivir administration was associated with higher mortality. These results were confirmed in an external validation cohort. Clustering algorithms may help physicians in decision-making processes to objectively personalize medicine. Finally, we created a clustering algorithm to classify patients with different viral loads. This algorithm can be used to reanalyze information obtained in trials or design future studies evaluating personalized antiviral strategies.

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Data Availability. All data generated or analyzed during this study are included as supplementary information files.

Declarations

Conflict of Interest. Carolina Garcia Vidal has received honoraria for talks on behalf of Gilead Science, MSD, Pfizer, Jannsen, Novartis, Basilea, GSK, Shionogi, AbbVie, Advanz Pharma, and a grant support from Gilead Science, Pfizer, GSK, MSD and Pharmamar. Alex Soriano has received honoraria for talks on behalf of Merck Sharp and Dohme, Pfizer, Novartis, and Angelini, as well as grant support from Pfizer. Alex Soriano is an Editor-in-Chief of *Infectious Diseases and Therapy*. Alex Soriano was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Olivier Peyrony has received honoraria for talks on behalf of BMS and Qiagen, and expertise for Sanofi. Other authors do not declare any conflict of interest.

Ethical Approval. The Institutional Ethics Committee of the Hospital Clinic of Barcelona approved the study and, as a result of the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

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