Clinical outcomes in patients infected with different SARS-CoV-2 variants at one hospital during three periods of the COVID-19 epidemic in Marseille, France

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Abstract (184/200 words)

Objectives: To compare the demographics, clinical characteristics and severity of patients infected with nine different SARS-CoV-2 variants, during three episodes of the COVID-19 epidemic in Marseille.

Methods: A single centre retrospective cohort study was conducted in patients infected with clade 20A, 20B, and 20C variants (first episode), the Marseille-2 and Marseille-4 variants (second episode), and the UK, Brazilian, Marseille-501 and South African variants (third episode). Outcomes were the occurrence of clinical failures, including hospitalisation, transfer to the intensive-care unit, and death.

Results: During each episode, no major differences were observed with regards to age and gender distribution, the prevalence of chronic diseases, and clinical symptoms between variants circulating in a given episode. The Marseille-2 and Marseille-4 variants were the most virulent. Infections occurring during the second episode were associated with a higher rate of death as compared to infections during the first and third episodes. Patients in the second episode were more likely to be hospitalised than those in the third episode. Patients infected during the third episode were more frequently obese than others.

Conclusion: A large cohort study is recommended to evaluate the transmissibility and to better characterise the virulence of emerging variants.

Keywords: COVID-19; SARS-CoV-2; variant; mutation; 501Y; Marseille

Highlights

- Monitoring the epidemiology of SARS-CoV-2 variants is very important for epidemic control
- During each episode, no major differences were observed between COVID-19 patients infected with variants circulating in a given episode
- Infections occurring during the second episode were associated with a higher rate of death as compared to infections during the first and third episodes
- No evidence of an increased risk for hospitalisation among patients infected with N501Y variant

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan in the Hubei province of China and causes the disease known as coronavirus disease 2019 (COVID-19). Since its emergence, SARS-CoV-2 has spread worldwide, and COVID-19 has caused the unprecedented disruption of human society. By 07 June 2021, the pandemic had infected nearly 160 million people and has led to the deaths of three million patients [1]. The presentation of the disease ranges from asymptomatic to severe and fatal forms, especially among older and vulnerable populations [2,3].

The diversity of the SARS-CoV-2 sequence was initially reported to be very low [4]. However, variants, which differ from all other strains by sets of several mutations, in contrast with mutants that result from the progressive accumulation of mutations during viral replication and spread, have been reported since summer 2020, including in our geographical area [5]. Recently, in late December 2020, new variants emerged, particularly those first described in the UK (named 20I/501Y.V1 or B.1.1.7), South Africa (20H/501Y.V2 or B.1.351) and Brazil (20J/501Y.V3 or P.1 variant) [6], which have become major concerns. Indeed, their spike protein, which is the target of immune responses elicited by previous infections or vaccine immunisation, harbour several amino acid substitutions, including N501Y and E484K, or deletions that confer decreased sensitivity to antibodies [7].

Preliminary reports in the UK suggest that the UK variant is more transmissible than previously circulating strains, with increased transmissibility estimated to be up to 75% [8]. The South African variant is also spreading rapidly in this country. In addition, both variants have spread to several countries located in six WHO regions (https://nextstrain.org/ncov/global) [9]. The SARS-CoV-2 variant – P.1, initially identified in Manaus, Amazonas State, Brazil is also spreading to various countries [9].

In Marseille, the first case of COVID-19 was recorded at the IHU Méditerranée Infection on 27 February 2020 and the epidemic was characterised by three major phases. The first (phase 1) started in February and almost ended in May [5,10]. The second episode occurred suddenly at the end of June and lasted until December 2020. The third phase started in January 2021 and is still ongoing at the time of writing. SARS-CoV-2 genomes were sequenced over time to characterise the genetic diversity of SARS-CoV-2. During the first phase of the epidemic, clade 20A (20AS), 20B (20BS) and 20C (20CS) variants, closely related to the initial Wuhan-Hu-1 strains, were predominantly circulating [10]. In January 2021, 14 variants, with clearly distinct genomic patterns, were concomitantly or successively spread in the Marseille area [10,11], with three variants, including Marseille-1 (M1V), Marseille-2 (M2V) and Marseille-4 (M4V), successively predominating [10,12]. The first case of the N501Y variant (N501YV) was diagnosed in our institute on 31 December 2020, starting the third phase of the epidemic in Marseille. The UK variant (UKV) was the main variant circulating during this third phase, followed by the Brazilian variant (BrV), the Marseille-501 variant (M-501V) [13] and the South African variant (SaV) (Figure 1). In a preliminary study, we observed that patients infected with 20AS, M1V, M4V and N501YV variants presented different patterns of symptoms and severity [5,10,11]. In this paper, we compare the demographics, clinical characteristics and severity of patients infected with nine different SARS-CoV-2 variants, during the three episodes of the COVID-19 epidemic in Marseille.

Material and Methods

Data source

We conducted a single centre retrospective cohort study at the Institut Hospitalier Universitaire (IHU) Méditerranée Infection, Marseille (France), which is part of the network of public hospitals in Marseille (AP-HM). All available SARS-CoV-2 genome sequences obtained by our laboratory between March 2020 and April 2021 were reviewed. Patients infected with clade 20AS, 20BS and 20CS (circulating during the first phase of epidemic), M2V or M4V (during the second phase), or different variants harbouring a N501YV substitution within the spike region (circulating during the third phase of pandemic), were selected (Figure 1). A second filter was applied to include only patients with information available on clinical status and follow-up. The M1V variant that reached a very weak peak but represented up to 100% of infections during part of the month of July and then disappeared after a month-and-a-half has been described elsewhere [10].

Patients

The IHU received patients or asymptomatic contacts directly presenting for SARS-CoV-2 testing or samples sent from other wards in the AP-HM (particularly in temporarily dedicated COVID-19 units and in intensive care units), or from laboratories outside the AP-HM. Most of the positive patients sampled at IHU were followed-up in the day clinic or were hospitalised in the Infectious Diseases department of the IHU, according to the severity of the disease. No detailed information was available for patients whose samples were sent to the IHU laboratory (Figure 2).

In this study, we only included patients who were seen at our institute in the day clinic or who were hospitalised in the conventional infectious disease units or other wards within the AP-HM. Demographic and clinical data including comorbidities were retrospectively retrieved from medical files including, notably, the main symptoms, in/outpatient status, transfer to intensive care unit (ICU), and death. At the time of writing, all patients had recovered and been discharged from hospital or had died. Because death could possibly occur long-time post-discharge, mortality was investigated through the national data on COVID-19 related mortality (at least 30 days post-discharge) [14]. Patients with missing information were mostly patients whose samples were send to our laboratory by external medical facilities and who were therefore excluded.

Genome sequencing and assembling

Samples that were positive for SARS-CoV-2, identified by real-time PCR [15] with a Ct-value <30, were processed for next-generation sequencing. Whole genome sequencing was performed as previously described [10] from 200 µL of nasopharyngeal swab fluid after viral RNA extraction with the EZ1 Virus Mini Kit v2.0, then reverse transcription by SuperScript IV (ThermoFisher Scientific, Waltham, MA, USA), cDNA second strand synthesis using Klenow Fragment DNA polymerase (New England Biolabs, Beverly, MA, USA), and generated DNA purification with Agencourt AMPure XP beads (Beckman Coulter, Villepinte, France). Genome next-generation sequencing used Illumina technology on a MiSeq instrument and the Illumina Nextera XT Paired end strategy (Illumina Inc., San Diego, CA, USA). Genome assembly was performed using the CLC Genomics workbench v.7 software by mapping on the SARS-CoV-2 genome GenBank Accession no. NC_045512.2 (Wuhan-Hu-1 isolate). Recovered genomes were compared to sequences from the GISAID database (https://www.gisaid.org/). Phylogeny reconstructions were performed with the GISAID TreeTool v2.0 (https://www.gisaid.org/epiflu-applications/upcoming-features-in-v20/treetool-app/).

Statistics

Statistical analyses were carried out using R [R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. URL: https://www.Rproject.org/] and Stata version 15.1 [http://www.stata.com]. Qualitative variables were presented by percentage. We used two approaches to conduct the analysis. The first examined the demographics and clinical profiles of patients infected with different strains or variants during each phase of the epidemic: clade 20AS vs. 20BS vs. 20CS (first phase), M2V vs. M4V (second phase) and UKV vs. SaV vs. BrV vs. M-501V (third phase). The second approach evaluated the difference in clinical outcomes, including hospitalisation, transfer to the ICU, and death among patients infected with SARS-CoV-2 variants during the three episodes (first episode vs. second episode vs. third episode). Unadjusted associations between multiple factors and groups of variants or clinical outcomes were examined by univariate analysis. Variables with p values <0.2 in the univariate analysis were included in the multivariate analysis [16]. The φ coefficient was used to test for multicollinearity among the independent variables. For pairs of variables that were highly correlated (absolute value of correlation coefficient >0.7), only one variable was entered into the multivariate model. Multivariate analysis was performed using exact logistic regression. The results were presented by percentages and odds ratio (OR), with a 95% confidence interval (95%CI). A p-value < 0.05 was considered as statistically significant.

Ethics Statement

Whole genome sequencing was performed on nasopharyngeal samples that were collected in the context of routine diagnosis. No additional samples were collected for this study. Clinical data were retrospectively retrieved from medical files and anonymised before analysis. Ethical approval was obtained from the Marseille Institutional Review Board and Ethics Committee (No. 2020-016-03).

Results

Between 29 February 2020 and 14 April 2021, we identified 3,993 COVID-19 patients infected with nine variants, the viral genomes of them were sequenced. Clinical data were available from 1,760 of these patients who were treated at our institute, including clade 20AS (N = 274), 20BS (N = 65), 20CS (N = 95) during the first episode, M2V (N = 69), M4V (N = 281) during the second episode, and UKV (N = 817), SaV (N = 98), BrV (N = 20) and M-501V (N = 41) during the third episode (Supplementary table S1).

Patients with clinical data were older than excluded patients (p<0.0001). No significant difference in gender was observed between the two groups (p=0.65) (Supplementary table S1).

Comparison of patients infected with clade 20AS, 20BS and 20CS during the first episode of the epidemic.

Table 1 shows the characteristics of 434 patients infected with the three major strains circulating during the first phase of the COVID-19 epidemic in Marseille.

In multivariate analysis, patients infected with clade 20AS and 20CS variants were significantly older than those infected with clade 20BS. Patients infected with the clade 20AS were significantly more likely to present with rhinitis than those infected with the clade 20BS and were less likely to report a cough than those infected with the clade 20CS. Patients infected with 20CS were less likely to present with dyspnoea than patients infected with 20AS and 20BS. No significant differences in clinical outcomes, including hospitalisation rate, transfer to the ICU, and death, was observed between patients infected with these three strains.

Comparison of patients infected with M2V and M4V variants during the second episode of the epidemic.

Table 2 shows the characteristics of 350 patients infected with the two major variants circulating during the second phase of the COVID-19 epidemic in Marseille.

In multivariate analysis, patients infected with M2V were less likely to be hospitalised than those infected with M4V. No significant differences in demographics, comorbidities, clinical profiles, transfer to the ICU, and mortality were observed.

Comparison of patients infected with UKV, SaV, BrV and M-501V during the third episode of the epidemic.

Table 3 shows the characteristics of 976 patients infected with the four major variants circulating during the third phase of the COVID-19 epidemic in Marseille.

Patients infected with UKV and SaV presented a relatively similar profile of demographic characteristics, comorbidities, and clinical symptoms in multivariate analysis (Table 4). Patients infected with BrV had a higher proportion of patients aged 45–64 years than those infected with UKV, SaV or M-501V. Patients infected with BrV were more likely to present with a cough than those infected with SaV and were more likely to report anosmia than those infected with the UKV and M-501V. No significant differences of clinical outcomes (hospitalisation, transfer to the ICU and death) were observed between patients infected with these four variants.

Comparison of COVID-19 patients during three episodes of the epidemic.

Table 5 shows the characteristics of 1,760 patients infected during the three episodes of the epidemic in Marseille.

In multivariate analysis, compared to patients in the first episode, those in the second episode were older and more likely to present with a fever, but less likely to report a cough and rhinitis Patients in the second episode were also more likely to die than those in the first phase. Compared to patients in first episode, patients infected during the third episode were significantly older and less likely to report chronic heart diseases but more likely to report obesity. They were more likely to present with a fever, but less likely to report rhinitis and ageusia. Finally, they were more frequently transferred to the ICU than those in the first episode. Compared to patients in the third episode, patients infected during the second episode were more likely to report chronic heart diseases but less likely to report obesity. They were more likely to report ageusia. Finally, they were more likely to be hospitalised and to die, but were less likely to be transferred to the ICU.

Discussion

SARS-CoV-2 is able to rapidly genetically diversify. Its variants can spread internationally through travellers and can cause successive outbreaks, with different clinical manifestations, even in populations who have previously been exposed to the original virus. In this study, we compared the demographics, clinical profile and outcomes of patients infected with different variants that circulated or continue to circulate in Marseille area, where three major episodes have occurred so far. During each episode, no major differences were observed with regards to age and gender distribution, the prevalence of chronic diseases, and clinical symptoms between variants circulating during a given episode. The overall comparison between the three episodes from March 2020 to April 2021 showed that the variants of the second episode (Marseille-2 and Marseille-4) were the most virulent, leading to higher rate of hospitalisation and death. The appearance of the N501Y variants at the end of December 2020 caught the attention of World Health Organization. This variant is known to spread faster than other variants and the original virus [8,9,17,18]. However, its virulence remains unclear. In studies based on a community-based testing dataset, this variant was significantly associated with increase in hospitalisation and death [19-21]. In contrast, in a clinical study, Frampton *et al.* showed that this variant was not associated with the severity of COVID-19 disease [18]. In addition, an analysis of UK COVID-19 Clinical Information Network data showed no risk of in-hospital deaths in patients infected with 501Y variant [22]. There was also no evidence of an increased risk for hospitalisation among patients infected with this variant [22]. Our observations corroborate other clinical studies. Patients infected during the third episode with variants harbouring the N501Y mutation were more frequently obese than others. This apparent higher likelihood of the NY501 variant to infect obese people needs further investigation in larger cohorts of individuals in order to be confirmed.

Monitoring the epidemiology of SARS-CoV-2 variants is very important for epidemic control. As of 11 May 2021, 46,251 SARS-CoV-2 replacements were identified (http://cov-glue.cvr.gla.ac.uk/#/replacement). Higher numbers of mutations are related to the NSP3 and S proteins with 9,414 (20.4%) and 6,238 (13.5%) variants, respectively. Recently, the B1.617 variant of SARS-CoV-2 emerged in Maharashtra, India and has since spread to at least 17 countries (https://www.gisaid.org/). At the time of writing only a few cases had been documented in Marseille [23]. The presentation and severity of the disease may be very different depending on the SARS-CoV-2 variants, so the public health response needs to be adapted in real-time to the genomic profile of each viral epidemic episode.

This work has some limitations. We did not evaluate the transmissibility of different variants. In addition, we only analysed patients seen at our hospitals (IHU and AP-HM wards), requiring medical care with a viral load allowing successful virus sequencing. This could introduce a major selection bias. A large proportion of patients were excluded from our analysis because they were not treated at either our Institute or within the AP-HM, and the actual severity of SARS-CoV-2 variants may differ from our results. Notably, the patients who were not included here were significantly younger and could have been asymptomatic or pauci-symptomatic. This selection bias is notably evidenced by the significantly higher hospitalisation, transfer to the ICU and mortality rates observed in patients whose virus sequence was available, as compared to those of the overall population of COVID-19 patients seen at our Institute with hospitalisation rates of about 18%, transfer to the ICU about 2%, and mortality of about 1% [24]. In addition, several biomarkers known to be associated with severity, including thrombopenia, D-dimer counts, troponin level and lactate dehydrogenase [25], were not considered in this analysis. Furthermore, we did not provide information on the duration of symptoms which could differ by variant.

Nevertheless, our study is the largest clinical study to date that compared the clinical profiles of nine lineages of SARS-CoV-2. A large cohort study is recommended to evaluate the transmissibility and better characterise the virulence of emerging variants.

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Conflicts of Interest

VTH, PC, AL, JD, JCL, PP, MM, PEF, DR and PG declare that they have no conflicts of interest.

Data availability statements

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Table 1: Characteristics of COVID-19 patients infected with clade 20A, 20B and 20C variants during the first episode of the epidemic in Marseille (univariate and multivariate analysis).

	20A		20B		20C		20A vs. 20B		20A vs. 20C		20B vs. 20C	
	n	%	n	%	n	%	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	N = 274		N = 65		N = 95		Ref = 20B		Ref = 20C		Ref = 20C	
Sociodemographic characteristic												
Mean age ± SD	49.1 ± 20.4		39.2 ± 17.2		48.9 ± 16.7		NA	NA	NA	NA	NA	NA
Age <45	126	46.0	44	67.7	34	35.8	ref	ref	ref	ref	ref	ref
45-64	92	33.6	14	21.5	45	47.4	2.29 [1.18 – 4.43] 0.01	2.44 [1.25 – 4.75] 0.009	0.55 [0.33 – 0.93] 0.03	**0.59** **[0.36 – 0.96]** **0.033**	0.24 [0.11 – 0.51] <0.0001	**0.22** **[0.10 – 0.48]** **<0.0001**
≥ 65	56	20.4	7	10.8	16	16.8	2.79 [1.19 – 6.58] 0.02	3.38 [1.40 – 8.14] 0.007	0.94 [0.48 – 1.85] 0.87	-	0.34 [0.13 – 0.91] 0.03	**0.33** **[0.12 – 0.91]** **0.033**
Gender Female	152	55.5	33	50.8	49	51.6	0.83 [0.46 – 1.48] 0.49	NA	0.85 [0.52 – 1.40] 0.51	NA	1.03 [0.52 – 2.04] 0.92	NA
Male	122	44.5	32	49.2	46	48.4						
Hypertension	56	20.4	5	7.7	18	19.0	3.08 [1.17 – 10.27] 0.02	-	1.10 [0.59 – 2.11] 0.75	NA	0.36 [0.10 – 1.08] 0.04	-
Diabetes	24	8.8	2	3.1	10	10.5	3.02 [0.72 – 27.01] 0.12	-	0.82 [0.36 – 1.99] 0.61	NA	0.27 [0.03 – 1.34] 0.08	-
Cancer	13	4.7	1	1.5	2	2.11	3.19 [0.46 – 137.53] 0.24	NA	2.32 [0.51 – 21.48] 0.26	NA	0.73 [0.01 – 14.26] 0.80	NA
Chronic respiratory disease	24	8.8	9	13.9	11	11.6	0.60 [0.25 – 1.55] 0.21	NA	0.73 [0.33 – 1.73] 0.42	NA	1.23 [0.42 – 3.49] 0.67	NA
Chronic heart disease	33	12.0	6	9.2	8	8.4	1.35 [0.52 – 4.11] 0.52	NA	1.49 [0.64 – 3.87] 0.33	NA	1.11 [0.30 – 3.85] 0.86	NA
Obesity	28	10.2	8	12.3	10	10.5	0.81 [0.33 – 2.17]	NA	0.97 [0.43 – 2.33]	NA	1.19 [0.38 – 3.59]	NA

							0.62		0.93		0.73	
Clinical signs												
Fever	75	27.4	20	30.8	23	24.2	0.85 [0.46 – 1.62] 0.58	NA	1.18 [0.67 – 2.13] 0.55	NA	1.39 [0.64 – 3.00] 0.36	NA
Cough	133	48.5	36	55.4	57	60.0	0.76 [0.42 – 1.35] 0.32	NA	0.63 [0.38 – 1.04] 0.054	**0.58** **[0.36 – 0.95]** **0.03**	0.83 [0.42 – 1.65] 0.56	NA
Rhinitis	113	41.2	21	32.3	34	35.8	1.47 [0.80 – 2.75] 0.19	**1.83** **[1.01 – 3.31]** **0.047**	1.26 [0.76 – 2.11] 0.35	NA	0.86 [0.41 – 1.76] 0.65	NA
Dyspnoea	79	28.8	18	27.7	15	15.8	1.06 [0.56 – 2.06] 0.86	NA	2.16 [1.15 – 4.28] 0.01	**2.35** **[1.26 – 4.39]** **0.007**	2.04 [0.88 – 4.79] 0.07	**2.42** **[1.05 – 5.58]** **0.038**
Anosmia	78	28.6	14	21.5	21	22.1	1.46 [0.74 – 3.02] 0.25	NA	1.41 [0.79 – 2.58] 0.22	NA	0.97 [0.41 – 2.21] 0.93	NA
Ageusia	73	26.7	16	24.6	20	21.1	1.12 [0.58 – 2.24] 0.73	NA	1.37 [0.76 – 2.54] 0.27	NA	1.22 [0.54 – 2.76] 0.60	NA
Hypoxemia	55	20.1	7	10.8	15	15.8	2.08 [0.88 – 5.69] 0.08	-	1.34 [0.70 – 2.70] 0.36	NA	0.64 [0.21 – 1.81] 0.37	NA
Clinical outcomes												
Hospitalisation	63	23.0	15	23.1	26	27.4	0.99 [0.51 – 2.04] 0.99	NA	0.79 [0.45 – 1.41] 0.39	NA	0.80 [0.35 – 1.75] 0.54	NA
ICU	5	1.8	1	1.5	3	3.2	1.19 [0.13 – 57.12] 0.87	NA	0.57 [0.11 – 3.75] 0.44	NA	0.48 [0.01 – 6.15] 0.52	NA
Death	11	4.0	2	3.1	3	3.2	1.32 [0.28 – 12.52] 0.72	NA	1.28 [0.33 – 7.31] 0.71	NA	0.97 [0.08 – 8.75] 0.98	NA

Ref: reference, NA: not applicable, -: non-significant

Table 2: Characteristics of COVID-19 patients infected with Marseille-2 and Marseille-4 variants during the second episode of the epidemic in Marseille (univariate and multivariate analysis).

	Marseille-2		Marseille-4		Marseille-2 v. Marseille-4	
	n	%	n	%	Univariate analysis	Multivariate analysis
	N = 69		N = 281		Ref = Marseille-4	
Sociodemographic characteristic						
Mean age	56.0 ± 21.6		58.3 ± 23.1		NA	NA
Age <45	24	34.8	74	26.3	ref	ref
45-64	19	27.5	88	31.3	0.67 [0.34 – 1.31] 0.24	NA
≥ 65	26	37.7	119	42.4	0.67 [0.36 – 1.26] 0.22	NA
Gender Female	38	55.1	127	45.2	0.67 [0.38 – 1.18] 0.14	-
Male	31	44.9	154	54.8		
Hypertension	17	24.6	86	30.6	0.74 [0.38 – 1.39] 0.33	NA
Diabetes	5	7.3	49	17.4	0.37 [0.11 – 0.98] 0.04	-
Cancer	8	11.6	27	9.6	1.23 [0.46 – 2.97] 0.62	NA
Chronic respiratory disease	5	7.3	37	13.2	0.52 [0.15 – 1.39] 0.18	-
Chronic heart disease	14	20.3	55	19.6	1.05 [0.50 – 2.08] 0.89	NA
Obesity	8	11.6	27	9.6	1.23 [0.46 – 2.97] 0.62	NA
Clinical signs						
Fever	27	39.1	121	43.1	0.85 [0.48 – 1.50] 0.55	NA
Cough	28	40.6	106	37.7	1.13 [0.63 – 1.99] 0.66	NA
Rhinitis	10	14.5	45	16.0	0.89 [0.38 – 1.92] 0.76	NA
Dyspnoea	17	24.6	71	25.3	0.97 [0.49 – 1.83] 0.91	NA

Anosmia	11	15.9	39	13.9	1.17 [0.51 – 2.51] 0.67	NA
Ageusia	9	13.0	38	13.6	0.96 [0.38 – 2.15] 0.91	NA
Hypoxemia	17	24.6	86	30.6	0.74 [0.38 – 1.39] 0.33	NA
Clinical outcomes						
Hospitalisation	21	30.4	129	45.9	0.52 [0.28 – 0.93] 0.02	**0.52** **[0.29 – 0.91]** **0.02**
ICU	2	2.9	16	5.7	0.49 [0.05 – 2.19] 0.35	NA
Death	8	11.6	44	15.7	0.71 [0.27 – 1.62] 0.40	NA

Ref: reference, NA: not applicable, -: non-significant

Table 3. Characteristics of COVID-19 patients infected with the UK, South African, Brazilian and Marseille 501 variants during the third phase of the epidemic in Marseille (univariate analysis).

	UK N = 817	SdA N = 98	Brazilian N = 20	Marseille 501 N = 41	Uk vs. SdA	Brazilian vs. UK	Brazilian vs. SdA	Marseille 501 vs. UK	Marseille 501 vs. SdA	Marseille 501 vs. Brazilian
	n (%)	n (%)	n (%)	n (%)	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value
					Ref = SdA	Ref = UK	Ref = SdA	Ref = UK	Ref = SdA	Ref = Brazilian
Sociodemographic characteristic										
Mean age	54.6 ± 17.5	52.9 ± 19.0	52.6 ± 13.7	56.0 ± 19.2	NA	NA	NA	NA	NA	NA
Age										
<45	229 (28.0)	29 (29.6)	3 (15.0)	12 (29.3)	ref	ref	ref	ref	ref	ref
45 – 64	340 (41.6)	39 (39.8)	15 (75.0)	15 (36.6)	1.10 [0.66 – 1.84] 0.70	3.37 [0.96 – 11.76] 0.06	3.72 [0.98 – 14.05] 0.053	0.84 [0.39 – 1.83] 0.66	0.93 [0.38 – 2.28] 0.87	0.25 [0.06 – 1.07] 0.06
≥ 65	248 (30.4)	30 (30.6)	2 (10.0)	14 (34.1)	1.05 [0.61 – 1.80] 0.87	0.62 [0.10 – 3.72] 0.60	0.64 [0.10 – 4.14] 0.64	1.08 [0.49 – 2.38] 0.85	1.13 [0.45 – 2.84] 0.80	1.75 [0.25 – 12.28] 0.57
Gender										
Female	404 (49.5)	48 (49.0)	8 (40.0)	22 (53.7)	ref	ref	ref	ref	ref	ref
Male	413 (50.5)	50 (51.0)	12 (60.0)	19 (46.3)	0.98 [0.63 – 1.53] 0.93	1.47 [0.54 – 4.18] 0.40	1.44 [0.49 – 4.43] 0.46	0.84 [0.43 – 1.66] 0.60	0.83 [0.37 – 1.83] 0.61	0.58 [0.17 – 1.93] 0.32
Hypertension	226 (27.7)	30 (30.6)	5 (25.0)	11 (26.8)	0.87 [0.54 – 1.42] 0.54	0.87 [0.25 – 2.56] 0.79	0.76 [0.20 – 2.46] 0.62	0.96 [0.43 – 2.01] 0.91	0.83 [0.33 – 2.00] 0.66	1.10 [0.28 – 4.79] 0.88
Diabetes	109 (13.3)	10 (10.2)	2 (10.0)	5 (12.2)	1.35 [0.68 – 3.01] 0.38	0.72 [0.08 – 3.08] 0.66	0.98 [0.10 – 5.20] 0.98	0.90 [0.27 – 2.38] 0.83	1.22 [0.31 – 4.26] 0.73	1.25 [0.18 – 14.29] 0.80
Cancer	54 (6.6)	6 (6.1)	0 (0)	4 (9.8)	1.09 [0.45 – 3.17] 0.85	NA	NA	1.53 [0.38 – 4.49] 0.43	1.66 [0.32 – 7.43] 0.45	NA
Chronic respiratory disease	100 (12.2)	12 (12.2)	2 (10.0)	1 (2.4)	1.00 [0.52 – 2.08] 1.00	0.80 [0.09 – 3.41] 0.76	0.80 [0.08 – 4.08] 0.78	0.18 [0.01 – 1.08] 0.06	0.18 [0.01 – 1.30] 0.07	0.23 [0.01 – 4.70] 0.19

Chronic heart disease	72 (8.8)	10 (10.2)	0 (0)	2 (4.9)	0.85 [0.42 – 1.92] 0.65	NA	NA	0.53 [0.06 – 2.13] 0.38	0.45 [0.05 – 2.28] 0.31	NA
Obesity	162 (19.8)	13 (13.3)	5 (25.0)	8 (19.5)	1.62 [0.87 – 3.24] 0.12	1.35 [0.38 – 2.78] 0.94	2.18 [0.53 – 7.76] 0.18	0.98 [0.38 – 2.22] 0.96	0.16 [0.52 – 4.57] 0.35	0.73 [0.17 – 3.34] 0.62
Clinical signs										
Fever	361 (44.2)	34 (34.7)	9 (45.0)	13 (31.7)	1.49 [0.94 – 2.38] 0.07	1.03 [0.37 – 2.78] 0.94	1.54 [0.51 – 4.53] 0.38	0.59 [0.27 – 1.19] 0.12	0.87 [0.37 – 2.02] 0.73	0.57 [0.17 – 1.98] 0.31
Cough	384 (47.0)	38 (38.8)	13 (65.0)	16 (39.0)	1.40 [0.89 – 2.21] 0.12	2.09 [0.77 – 6.26] 0.11	2.93 [0.97 – 9.42] 0.03	0.72 [0.35 – 1.43] 0.32	1.01 [0.44 – 2.27] 0.98	0.34 [0.10 – 1.19] 0.06
Rhinitis	176 (21.5)	16 (16.3)	3 (15.0)	10 (24.4)	1.41 [0.79 – 2.64] 0.23	0.64 [0.12 – 2.26] 0.48	0.90 [0.15 – 3.70] 0.88	1.17 [0.50 – 2.52] 0.67	1.65 [0.60 – 4.36] 0.27	1.83 [0.39 – 11.62] 0.40
Dyspnoea	211 (25.8)	25 (25.5)	4 (20.0)	7 (17.1)	1.02 [0.62 – 1.72] 0.95	0.72 [0.17 – 2.26] 0.56	0.73 [0.16 – 2.57] 0.60	0.59 [0.22 – 1.38] 0.21	0.60 [0.20 – 1.62] 0.28	0.82 [0.18 – 4.42] 0.78
Anosmia	91 (11.1)	15 (15.5)	7 (35.0)	2 (4.9)	0.69 [0.37 – 1.34] 0.21	4.30 [1.41 – 11.91] 0.001	2.94 [0.84 – 9.53] 0.04	0.41 [0.05 – 1.63] 0.21	0.28 [0.03 – 1.31] 0.08	0.10 [0.01 – 0.61] 0.002
Ageusia	83 (10.2)	12 (12.4)	5 (25.0)	2 (4.9)	0.80 [0.41 – 1.68] 0.50	2.95 [0.82 – 8.80] 0.03	2.36 [0.56 – 8.54] 0.14	0.45 [0.05 – 1.81] 0.27	0.36 [0.04 – 1.76] 0.18	0.15 [0.01 – 1.10] 0.02
Hypoxemia	199 (24.4)	30 (30.6)	3 (15.0)	11 (26.8)	0.73 [0.45 – 1.20] 0.18	0.55 [0.10 – 1.92] 0.33	0.40 [0.07 – 1.55] 0.16	1.14 [0.51 – 2.39] 0.72	0.83 [0.33 – 2.00] 0.66	2.08 [0.45 – 13.05] 0.30
Clinical outcomes										
Hospitalisation	203 (24.9)	31 (31.6)	4 (20.0)	11 (26.8)	0.71 [0.45 – 1.17] 0.15	0.76 [0.18 – 2.38] 0.62	0.54 [0.12 – 1.88] 0.30	1.11 [0.49 – 2.33] 0.77	0.79 [0.32 – 1.89] 0.57	1.47 [0.35 – 7.31] 0.56
ICU	58 (7.1)	9 (9.2)	2 (10.0)	2 (4.9)	0.76 [0.36 – 1.80] 0.45	1.45 [0.16 – 6.31] 0.62	1.10 [0.11 – 5.98] 0.91	0.67 [0.08 – 2.71] 0.59	0.51 [0.05 – 2.63] 0.39	0.46 [0.03 – 6.93] 0.45
Death	34 (4.2)	0 (0)	0 (0)	4 (9.8)	NA	NA	NA	2.49 [0.61 – 7.52] 0.09	NA	NA

SdA: South African, Ref: reference, NA: not applicable

Table 4. Characteristics of COVID-19 patients infected with the UK, South Africa, Brazilian and Marseille 501 variants during third phase of the epidemic in Marseille (multivariate analysis).

	UK vs SdA	Brazilian vs. UK	Brazilian vs. SdA	Marseille 501 vs. UK	Marseille 501 vs SdA.	Marseille 501 vs. Brazilian
	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value	OR [95%CI] P-value
	Ref = SdA	Ref = UK	Ref = SdA	Ref = UK	Ref = SdA	Ref = Brazilian
Sociodemographic characteristic						
Age						
<45	NA	ref	ref	ref	ref	ref
45 – 64	NA	**4.21 [1.51 – 11.77] 0.006**	**4.89 [1.59 – 14.98] 0.005**	NA	NA	**0.24 [0.07 – 0.83] 0.03**
≥ 65	NA	-	NA	NA	NA	-
Gender						
Female						
Male	NA	NA	NA	NA	NA	NA
Hypertension	NA	NA	NA	NA	NA	NA
Diabetes	NA	NA	NA	NA	NA	NA
Cancer	NA	NA	NA	NA	NA	NA
Chronic respiratory disease	NA	NA	NA	-	-	-
Chronic heart disease	NA	NA	NA	NA	NA	NA
Obesity	-	NA	-	NA	NA	NA
Clinical signs						
Fever	-	NA	NA	-	NA	NA
Cough	-	-	**3.24 [1.13 – 9.28] 0.028**	NA	NA	-
Rhinitis	NA	NA	NA	NA	NA	NA
Dyspnoea	NA	NA	NA	NA	NA	NA
Anosmia	NA	**4.30 [1.66 – 11.19] 0.003**	-	NA	-	**0.12 [0.02 – 0.73] 0.02**
Ageusia	NA	-	-	NA	-	-
Hypoxemia	-	NA	-	NA	NA	NA
Clinical outcomes				NA	NA	
Hospitalisation	-	NA	NA	NA	NA	NA
ICU	NA	NA	NA	NA	NA	NA
Death	NA	NA	NA	-	NA	NA

SdA: South African, Ref: reference, NA: not applicable, -: non-significant

Table 5: Characteristics of COVID-19 patients during the three episodes of the epidemic in Marseille (univariate and multivariate analysis).

	First episode		Second episode		Third episode		Second episode vs. first episode		Third episode vs. first episode		Second episode vs. third episode	
			N = 350		N =							
	n	%	n	%	n	%	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	N = 434		N = 350		N = 976		Ref = first episode		Ref = first episode		Ref = third episode	
Sociodemographic characteristic												
Mean age	47.5 ± 19.5		57.8 ± 22.8		54.4 ± 17.7		NA	NA	NA	NA	NA	NA
Age <45	204	47.0	98	28.0	273	28.0	ref	ref	ref	ref	ref	ref
45-64	151	34.8	107	30.6	409	41.9	1.48 [1.04 – 2.08] 0.03	-	2.02 [1.56 – 2.63] <0.0001	**1.75 [1.32 – 2.30] <0.0001**	0.73 [0.53 – 0.99] 0.048	-
≥ 65	79	18.2	145	41.4	294	30.1	3.82 [2.65 – 5.50] <0.0001	**2.20 [1.54 – 3.14] <0.0001**	2.78 [2.04 – 3.78] <0.0001	**2.45 [1.71 – 3.49] <0.0001**	1.37 [1.01 – 1.86] 0.04	-
Gender Female	234	53.9	165	47.1	482	49.4	ref	ref	ref	ref	ref	ref
Male	200	46.1	185	52.9	494	50.6	1.31 [0.98 – 1.76] 0.06	-	1.20 [0.95 – 1.51] 0.12	-	1.09 [0.85 – 1.41] 0.47	NA
Hypertension	79	18.2	103	29.4	272	27.9	1.87 [1.32 – 2.66] 0.0002	-	1.74 [1.30 – 2.33] 0.0001	-	1.08 [0.82 – 1.42] 0.58	NA
Diabetes	36	8.3	54	15.4	126	12.9	2.01 [1.17 – 3.25] 0.002	-	1.64 [1.10 – 2.49] 0.01	-	1.23 [0.85 – 1.76] 0.24	NA
Cancer	16	3.7	35	10.0	64	6.6	2.90 [1.53 – 5.71] 0.0004	-	1.83 [1.03 – 3.44] 0.03	-	1.58 [0.99 – 2.48] 0.04	-
Chronic respiratory disease	44	10.1	42	12.0	115	11.8	1.21 [0.75 – 1.94] 0.41	NA	1.18 [0.81 – 1.75] 0.37	NA	1.02 [0.68 – 1.50] 0.91	NA
Chronic heart disease	47	10.8	69	19.7	84	8.6	2.02 [1.33 – 3.09] 0.0005	-	0.78 [0.52 – 1.16] 0.18	**0.40 [0.26 – 0.61] <0.0001**	2.61 [1.81 – 3.73] <0.0001	**1.83 [1.23 – 2.70] 0.003**
Obesity	46	10.6	35	10.0	188	19.3	0.94 [0.57 – 1.53]	NA	2.01 [1.41 – 2.91]	**1.88 [1.31 – 2.70]**	0.47 [0.31 – 0.69]	**0.45 [0.30 – 0.67]**

							0.78		0.0001	**0.001**	0.0001	**<0.0001**
Clinical signs												
Fever	118	27.2	148	42.3	417	42.7	1.96 [1.44 – 2.68] <0.0001	**2.27** **[1.60 – 3.11]** **<0.0001**	2.00 [1.55 – 2.58] <0.0001	**1.94** **[1.50 – 2.52]** **<0.0001**	0.98 [0.76 – 1.27] 0.89	NA
Cough	226	52.1	134	38.3	451	46.2	0.57 [0.42 – 0.77] 0.0001	**0.69** **[0.50 – 0.96]** **0.03**	0.79 [0.63 – 0.99] 0.04	-	0.72 [0.56 – 0.93] 0.01	-
Rhinitis	168	38.7	55	15.7	205	21.0	0.30 [0.20 – 0.42] <0.0001	**0.37** **[0.26 – 0.54]** **<0.0001**	0.42 [0.33 – 0.54] <0.0001	**0.51** **[0.39 – 0.67]** **<0.0001**	0.70 [0.50 – 0.98] 0.03	-
Dyspnoea	112	25.8	88	25.1	247	25.3	0.97 [0.69 – 1.35] 0.83	NA	0.97 [0.75 – 1.27] 0.84	NA	0.99 [0.74 – 1.32] 0.95	NA
Anosmia	113	26.1	50	14.3	115	11.8	0.47 [0.32 – 0.69] 0.0001	-	0.38 [0.28 – 0.51] <0.0001	-	1.25 [0.86 – 1.81] 0.22	NA
Ageusia	109	25.2	47	13.5	102	10.5	0.46 [0.31 – 0.68] <0.0001	-	0.35 [0.25 – 0.47] <0.0001	**0.46** **[0.34 – 0.64]** **<0.0001**	1.33 [0.90 – 1.95] 0.13	**1.73** **[1.18 – 2.54]** **0.005**
Hypoxemia	77	17.7	103	29.4	243	24.9	1.93 [1.36 – 2.75] 0.0001	-	1.54 [1.15 – 2.07] 0.003	-	1.26 [0.95 – 1.66] 0.10	-
Clinical outcomes												
Hospitalisation	104	24.0	150	42.9	249	25.5	2.38 [1.73 – 3.27] <0.0001	-	1.09 [0.83 – 1.43] 0.54	NA	2.19 [1.68 – 2.85] <0.0001	**1.98** **[1.43 – 2.74]** **<0.0001**
ICU	9	2.1	18	5.1	71	7.3	2.56 [1.07 – 6.55] 0.02	-	3.70 [1.82 – 8.51] 0.0001	**2.30** **[1.11 – 4.78]** **0.03**	0.69 [0.38 – 1.19] 0.17	**0.32** **[0.18 – 0.58]** **<0.0001**
Death	16	3.7	52	14.9	38	3.9	4.56 [2.50 – 8.71] <0.0001	**1.91** **[1.02 – 3.59]** **0.04**	1.06 [0.57 – 2.06] 0.85	NA	4.31 [2.72 – 6.86] <0.0001	**3.01** **[1.81 – 5.01]** **<0.0001**

Ref: reference, NA: not applicable, -: non-significant

Figure 1: Weekly distribution of SARS-CoV-2 genotypes

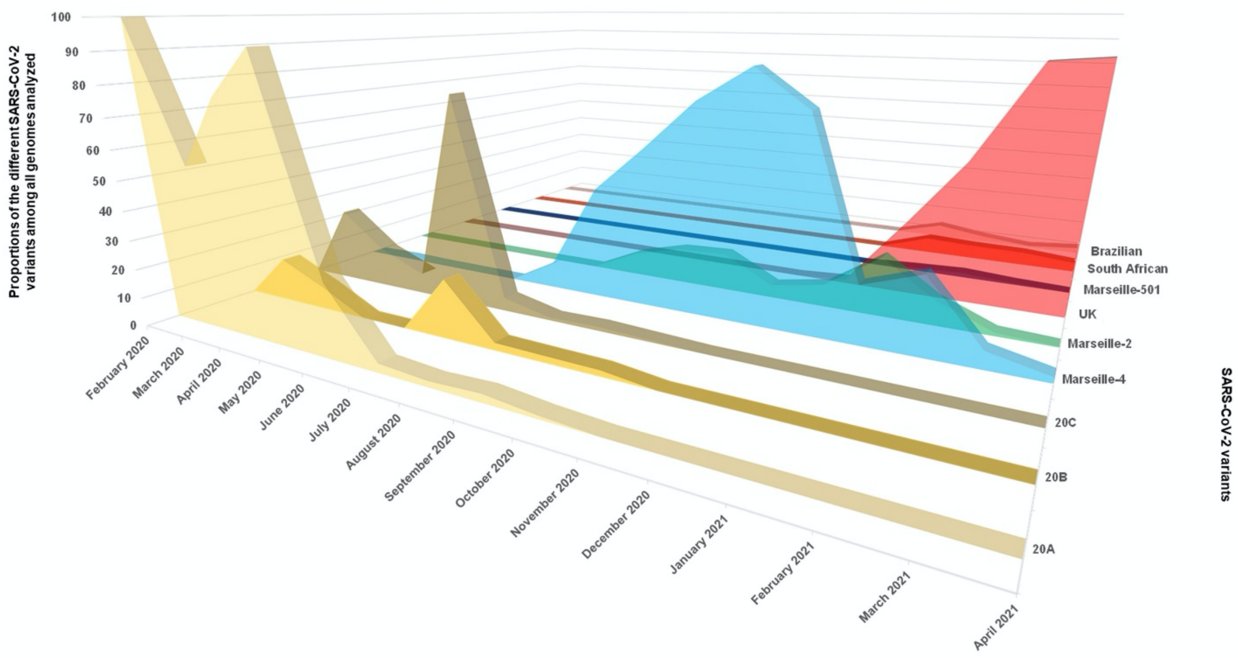
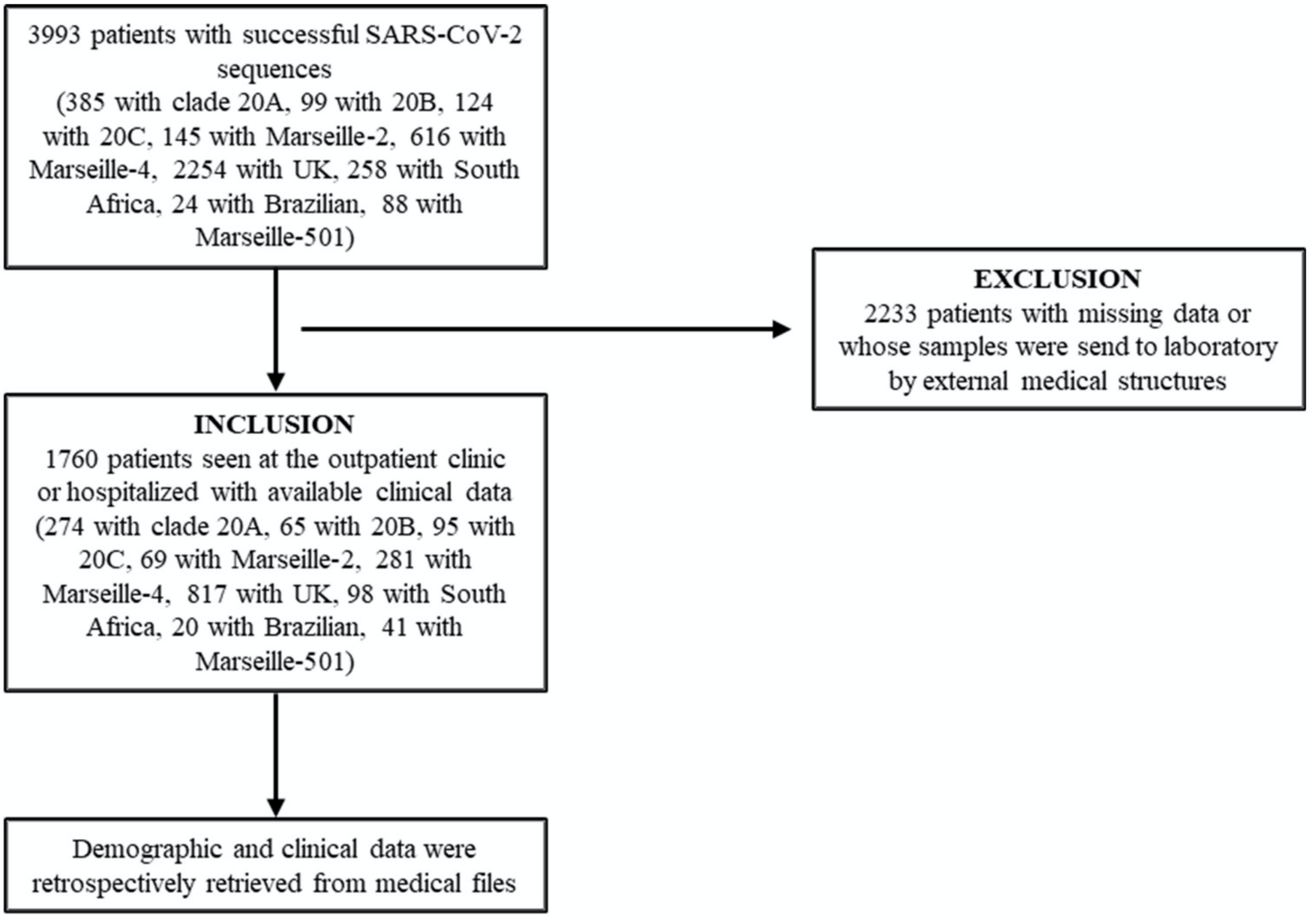


Figure 2: Flow-chart of study



Supplementary data

Supplementary Table S1: Age and gender in patients with available clinical data and in those excluded from the study.

	Total		Included patients (N = 1,760)		Excluded patients* (N = 2,233)		p-value**
	n	%	n	%	n	%	
Age							
Mean ± SD	47.0 ± 19.6		53.4 ± 19.6		41.9 ± 20.4		**<0.0001**
Range	0 - 109		0 - 99		0 - 109		
Age group							
<45	1853	46.4	575	32.7	1278	57.2	**<0.0001**
45 - <65	1320	33.1	667	37.9	653	29.3	
≥65	820	20.5	518	29.4	302	13.5	
Gender							
Female	2015	50.5	881	50.1	1134	50.8	0.65
Male	1978	49.5	879	49.9	1099	49.2	

*Patients that were not followed at IHU or other AP-HM wards

** Patients with clinical data versus excluded patients