SARS CoV-2 Genomic Characteristics and Clinical Impact of SARS-CoV-2 Viral Diversity in Critically Ill COVID-19 Patients: A Prospective Multicenter Cohort Study

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Abstract

Background: SARS-CoV-2 variant of concern (VOC) α spread worldwide, including in France, at the beginning of 2021. This variant was suggested to be associated with a higher risk of mortality than other variants. Little information is available in the subset of patients with severe disease admitted in the intensive care unit (ICU). We aimed to characterize the genetic diversity of SARS-CoV-2 variants isolated from patients with severe COVID-19 in order to unravel the relationships between specific viral mutations/mutational patterns and clinical outcomes.

Methods: Prospective multicentre observational cohort study. Patients aged ≥ 18 years admitted in 11 ICUs from Great Paris area hospitals between October 1, 2020, and May 30, 2021 (before the introduction of VOC δ (B.617.2) in France) for acute respiratory failure ($\text{SpO}_2 \leq 90\%$ and need for supplemental oxygen or ventilator support) were included. SARS-CoV-2 infection, determined by RT-PCR testing. The primary clinical endpoint was day-28 mortality. Full-length SARS-CoV-2 genomes were sequenced by means of next-generation sequencing (Illumina COVIDSeq).

Results: 413 patients were included, 183 (44.3%) had been infected with pre-existing variants, 197 (47.7%) with variant α (B.1.1.7), and 33 (8.0%) with other variants. Patients infected with pre-existing variants were significantly older (64.9 ± 11.9 vs 60.5 ± 11.8 years; $p=0.0005$); they had significantly more frequent COPD (11.5% ($n=21/183$) vs 4.1% ($n=8/197$); $p=0.009$), and higher SOFA score (4 [3-8] vs 3 [2-4]; 0.0002). Day-28 mortality was not different between patients infected with pre-existing, α (B.1.1.7) or other variants (31.1% ($n=57/183$) vs 26.2% ($n=51/197$) vs 30.3% ($n=10/33$), respectively; $p=0.550$). There was no association between day-28 mortality with a specific variant or the presence of specific mutations in SARS CoV-2 genome, including 17 mutations selected in the spike protein and all 1017 non-synonymous mutations detected throughout the entire viral genome.

Conclusions: At ICU admission, patients infected with pre-existing variants had a different clinical presentation from those infected with variant α (B.1.1.7) and other variants later in the course of the pandemic, but mortality did not differ between these groups. There was no association between a specific variant or SARS CoV-2 genome mutational pattern and day-28 mortality.

Background

As SARS-CoV-2 evolves and new variants continuously emerge worldwide, sustained monitoring and rapid assessment of genetic changes are required to inform the public health response and health-care management of COVID-19. Since the fall of 2020, the emergence of so-called SARS-CoV-2 “variants of concern” (VOC) and of several “variants of interest” (VOI) appears to result from the adaptation of the virus, combined with strong selective pressures on viral spreading in the context of ongoing collective immunization [1]. Many of the substitutions selected so far are located in the Spike (S) protein, the protein involved in viral attachment and entry into cells and the target of neutralizing antibodies.

SARS-CoV-2 VOC bearing multiple signature (lineage defining) deletions and amino-acid substitutions, such as N501Y and/or E484K (variants α (B.1.1.7), β (B.1.351) and γ (P.1)) have spread worldwide, including in France, in early 2021 and onwards. These changes have been suggested to result in increased infectivity, with 50–74% increased transmissibility for VOC α (B.1.1.7). More recently, variant δ (B.1.617.2) carrying L452R, T478K and P681R substitutions, with enhanced transmissibility compared to other VOC, has spread and replaced most circulating variants in many parts of the world. Beyond transmissibility and immune evasion, the viral factors that explain the severity of infection and the corresponding case-fatality rate in some patients remain unclear. Mutations located outside of the Spike gene in the SARS-CoV-2 genome have been suggested to contribute to enhanced virulence, but

these results have not been confirmed in other studies [2–4]. Similarly, the specific role of each VOC in the severity of the disease remains debated. In a preclinical Syrian golden hamster model, animals infected with variant α (B.1.1.7) produced significantly higher levels of proinflammatory cytokines than those infected with other variants, but there was no evidence for an altered phenotype [5]. In clinical settings, preliminary analyses of prognosis in patients infected with variant α (B.1.1.7) have suggested that this variant could be associated with a higher risk of mortality compared with infection with other variants [6,7]. By contrast, other studies found no association between mortality and infection with variant α (B.1.1.7) in patients admitted to hospital [8]. Very few clinical studies have evaluated whether being infected with VOC and VOI could modify the prognosis in the subset of patients with severe disease admitted in the intensive care unit (ICU) [9].

Most of prognostic studies describing the role of VOC compared to pre-existing variants were based on PCR-based screening tests, such as S-gene molecular diagnostic assay failure (SGTF) for variant α (B.1.1.7) [6,9,10], which did not discriminate different variants sharing the same pattern of mutations and could not evaluate the association of mutational hotspots with clinical outcomes. Genomic surveillance by means of full-length viral genome sequencing has become critical to identify circulating variants and the evolution of SARS-CoV-2 genomes over time. Different variants, including VOC and VOI circulate at the same time and their effects on disease severity and on the prognosis of severe forms remain unknown. At a mutational level, the presence of a single substitution (*e.g.* E484K) or a panel of mutations/deletions could specifically modulate the immune response, with a potential impact on the clinical course of the disease [11].

In this study, we aimed to characterize the genetic diversity of SARS-CoV-2 variants involved in severe COVID-19 cases, in a population of patients hospitalized in ICUs for acute respiratory failure following severe SARS-CoV-2 infection between October 2020 and May 2021, *i.e.*, before the emergence and spread of variant δ (B.617.2) in France. We further aimed to unravel the relationships between specific viral mutations/mutational patterns and the clinical outcomes of COVID-19 in these patients.

Patients And Methods

Study design and patients

This is a prospective multicentre observational cohort study. Patients admitted between October 1, 2020 (week 40/20) and May 30, 2021 (week 21/21) in one of the 11 participating ICUs from the Great Paris area hospitals and included in the ANTICOV study (NCT04733105) were eligible for study inclusion. Inclusion criteria were as follows : age ≥ 18 years, SARS-CoV-2 infection confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR), patient admitted in the ICU for acute respiratory failure ($\text{SpO}_2 \leq 90\%$ and need for supplemental oxygen or any kind of ventilator support), patient or next of kin informed of study inclusion. Patients with SARS-CoV-2 infection but no acute respiratory failure or with a PCR cycle threshold (Ct) >32 in nasopharyngeal samples were not included in the study. The study was approved by the Comité de Protection des Personnes Nord-Ouest IV (N° EudraCT/ID-RCB : 2020-A03009-30). Informed consent was obtained from all patients or their relatives.

Demographics, clinical and laboratory variables were recorded upon ICU admission and during ICU stay. Patients' frailty was assessed using the Clinical Frailty Scale [12]. The severity of the disease upon ICU admission was assessed using the World Health Organization (WHO) 10-point ordinal scale [13], the sequential organ failure assessment (SOFA [14]) score, and the simplified acute physiology score (SAPS) II score [15]. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [16]. The primary clinical endpoint of the study was day-28 mortality.

SARS-CoV-2 genome sequence analysis

The full-length SARS-CoV-2 genomes from all included patients were sequenced by means of next-generation sequencing. Briefly, viral RNA was extracted from nasopharyngeal swabs in viral transport medium using NucliSENS® easyMAG kit on EMAG device (bioMérieux, Marcy-l'Étoile, France). Sequencing was performed with the Illumina COVIDSeq Test (Illumina, San Diego, California), that uses 98-target multiplex amplifications along the full SARS-CoV-2 genome. The libraries were sequenced with NextSeq 500/550 High Output Kit v2.5 (75 Cycles) on a NextSeq 500 device (Illumina). The sequences were demultiplexed and assembled as full-length genomes by means of the DRAGEN COVIDSeq Test Pipeline on a local DRAGEN server (Illumina). Lineages and clades were interpreted using Pangolin and NextClade, before being submitted to the GISAID database (<https://www.gisaid.org>). Phylogeny was performed after full-length genome alignment with Muscle v3.8.31 (maximum-likelihood model GTR+I; 1000 bootstrap replicates), by means of IQ-Tree v1.3.11.1 and iTOL.

Statistical Analysis

Descriptive results are presented as means ($\pm$ standard deviation [SD]) or medians (1st-3rd tertiles) for continuous variables, and as numbers with percentages for categorical variables. Two-tailed p-values < 0.05 were considered statistically significant. Unadjusted comparisons between the main variants were performed using ANOVA or Kruskal-Wallis tests for global comparisons of continuous variables, and Chi² or Fisher's exact tests for categorical variables, as appropriate. In case of global significance, post-hoc pairwise comparisons were performed using t-tests or Mann-Whitney tests for continuous variables, and Chi² or Fisher's exact tests for categorical variables, as appropriate, applying a Sidak correction to account for multiple testing. Adjusted analyses of the association between variants or mutations and 28- and 90-day mortality relied on logistic regression models, systematically adjusting for age, SOFA score at admission, gender and dexamethasone treatment, computing adjusted odds ratios (ORa) along with their 95% confidence intervals. Analyses were performed using Stata V16.0 statistical software (StataCorp, College Station, TX, USA), and R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between October 1, 2020, and May 30, 2021, 845 patients were admitted in one of the 11 participating ICUs. Among them, 737 had at least one positive SARS-CoV-2 RNA RT-PCR performed in a nasopharyngeal swab sample in the hospital; 413 patients with a Ct $\leq$ 32 and a nasopharyngeal sample conserved at -80°C that could be used for full-length viral genome sequence analysis were included in this study. Among these 413 patients, 183 (44.3%) had been infected with so-called "pre-existing" variants, *i.e.*, variants circulating before the emergence of variant α , 197 (47.7%) with variant α (B.1.1.7), and 33 (8.0%) with other variants, including β (B.1.351) (n=19, 4.6%), γ (P.1) (n=2, 0.5%) and other variants of interest (n=12, 2.9%). **Figure 1** illustrates the time course of emerging SARS-CoV-2 variants during the study period. Variant α (B.1.1.7) was first detected during the last week of 2020 in 11.1% of patients, became predominant during the fourth week of January 2021 (51.9% of patients) and remained so until the last week of May (100% of patients) that corresponded to the end of the inclusion period.

SARS-CoV-2 variant association with clinical phenotypes at ICU admission

Patients infected with pre-existing variants were older and had significantly more frequent chronic kidney disease and COPD than those infected with other variants (**Table 1**). Other comorbidities, including diabetes, peripheral vascular disease, solid cancer, and hypertension followed the same trend, although differences were not statistically different.

There were also marked differences between variant groups regarding severity of disease at ICU admission. Indeed, patients infected with preexisting variants exhibited significantly higher severity of illness scores, with not only more severe respiratory disease, as assessed by the respiratory component of the SOFA score, but also more frequent extra-pulmonary organ failures, as compared with patients infected with variant α (B.1.1.7) and other emerging variants (**Table 1** and **Figure 2**). As a result, patients infected with pre-existing variants received less frequent high-flow oxygen therapy and more frequent extracorporeal membrane oxygenation (ECMO) support than other patients within the first 24 hours of ICU admission, while they more frequently met the ARDS definition criteria.

Relationship between SARS-CoV-2 variants and patient outcomes

Although patients infected with pre-existing variants were older, had more comorbidities and had more severe diseases at ICU admission, they did not show different outcomes from those infected with other variants. Overall, the need for invasive mechanical ventilation or ECMO support did not significantly differ between the different variant groups, nor did the duration of these supports. There were also no significant differences between groups regarding extra-pulmonary organ supports (*i.e.*, vasopressors and renal replacement therapy) during ICU stay (**Table 2**). Patients with pre-existing variants received less dexamethasone and tocilizumab than others, likely reflecting the changes in practice during the study period. As shown in **Table 2**, day-28 and day-90 mortality rates were not statistically different between groups.

Relationship between SARS-CoV-2 Spike substitutions and deletions and mortality

Pre-existing and emerging variants (VOC or VOI) are characterized by multiple lineage-specific deletions and amino-acid substitutions. Spike mutations undergo evolute convergence at several signature sites. Spike mutations at sites identified to undergo convergent mutational evolution were selected *a priori*. There was no significant relationship between any of these mutations ($n=17$) and day-28 mortality in univariate analysis (**Figure 3**). The selected mutations were also included in multivariate logistic regression models to determine their relationship with day-28 (**Table 3**) and day-90 (**Supplemental Table 1**) mortality, adjusting on age, gender, SOFA score at ICU admission, and dexamethasone treatment. None of them was significantly associated with mortality at either time point. The variant status was not either associated with mortality.

Relationship between SARS-CoV-2 spike and other gene mutation hotspots and mortality

Overall, 1017 non-synonymous mutations (including 953 amino acid substitutions, 52 deletions and 11 insertions) were detected in full-length viral genomes in at least one variant. There was no significant relationship between any of these mutations and day-28 mortality in univariate analysis (**Supplemental Table 2**). Although 11 mutations were found to be associated with mortality ($p<0.05$), the number of patients harboring these mutations was considered too small (range: 2-6) to drive conclusions.

We then focused on mutations previously reported to correlate with worse clinical outcomes [2,4,17]. We found that Q57H in Orf3a (but not other mutations, including P25L in Orf3a and S194L, R203K or G204R in N) was highly prevalent in our cohort (31.8%). Q57H was more prevalent in patients who were dead at day-28 (35.6%) than in those who were still alive, but the difference did not reach significance (29.0%; $p=0.196$).

Discussion

The full-length SARS-CoV-2 genomes of 413 critically ill COVID-19 patients from 11 ICUs, who were predominantly infected with pre-existing and α (B.1.1.7) variants, were sequenced and the relationship between viral sequences and

their clinical presentation and outcomes was studied. The main results of this study are the following: (i) as compared with others, patients infected with pre-existing variants showed a different clinical phenotype at ICU admission, characterized by an older age, more comorbidities and a more severe clinical presentation; (ii) despite these different initial clinical presentations, there were no significant differences in day-28 and day-90 mortality between the different SARS-CoV-2 variant groups; (iii) there was no statistically significant relationship between the presence of any of 17 relevant spike substitutions and deletions selected *a priori* and mortality; and (iv) a comprehensive full-length SARS-CoV-2 genome sequence analysis exploring all found mutations failed to identify a relationship between the presence of any of them and day-28 mortality.

Patients infected with variants pre-existing the emergence of variant α at the end of 2020 showed significant clinical differences, including an older age and more comorbidities, when compared with patients infected with other variants, in particular variant α (B.1.1.7), a result in keeping with those from previous cohorts [8–10]. Importantly, our results show differences in clinical severity of the disease resulting in different organ support requirements during the first 24 hours of management in the ICU in patients infected with different SARS-CoV-2 variants. Indeed, patients infected with pre-existing variants exhibited more severe pulmonary and non-pulmonary organ failures than those infected with variant α (B.1.1.7). Surprisingly, although admission severity of illness scores (*i.e.*, SAPS II [15] and SOFA [14]) predicted higher mortality in patients infected with pre-existing variants, there was no significant difference in mortality rates when compared to patients infected with variant α (B.1.1.7). This finding, together with the fact that patients infected with variant α (B.1.1.7) reached similar organ support requirements during their ICU stay (Table 2), indicates that the severity of disease and the time course of organ failures have been delayed in patients infected with variant α , as compared to patients infected with pre-existing variants. Whether this different time course should be ascribed to host-related factors (*e.g.*, age, comorbidities), a different pathogenesis/virulence of the variant, or differences in the type of patient management is unclear. Previous large-scale data have suggested that patients infected with variant α (B.1.1.7), identified using the SGTF proxy, had a higher risk of dying [6,9,10]. However, in the study by Frampton *et al.*, which included 341 hospitalized patients, no association was found between the severity of the disease, death and the viral lineage [8]. Interestingly, following SARS-CoV-2-infected patients with different disease severities through the pathway of disease management, Grint *et al.* reported a weakening association between variant α (B.1.1.7) infection and mortality, highest in the primary care population, lower in the hospitalized population, non-significant in patients admitted in the ICU [10]. Indeed, other determinants of COVID-19 mortality, including male gender, age, and associated comorbidities have been shown to have a major impact on the outcome [18]. Our results are thus not in contradiction with previous studies showing an increased mortality associated with variant α (B.1.1.7) in the community [6,9]. They are in keeping with data specific to ICU patient populations [9,10].

Spike mutations have dominated SARS-CoV-2 variant research, owing to concerns regarding enhancement of viral replication and transmission via ACE-2 receptor binding and/or lower sensitivity to the action of naturally or vaccine-induced neutralizing antibodies. In contrast, little attention has been paid to variant-specific mutations in other viral proteins. Nevertheless, such mutations could be associated with different clinical outcomes. Previous large-scale studies based on the GISAID database and *in vitro* experiments suggested that amino acid substitutions in the N and Orf3a regions could be associated with more severe disease. To study the potential link between SARS-CoV-2 genetic diversity outside of the spike protein and severe COVID-19 cases outcomes, we analyzed all non-synonymous mutations in the full-length SARS-CoV-2 genomes and not only assessed the relationship between variant status and mortality, as already performed by others [6,8–10], but also performed a mutational analysis of all viral genes. None of the pre-selected relevant spike substitutions/deletions ended up being associated with mortality, either in univariate or in multivariate analyses. When extending the analysis to all viral genes, we found 11

mutations that were harbored by a very small number of patients ($n \leq 6$) with a statistically significant difference but without clinically relevant meaning. Together, our results indicate that in patients with the most severe forms of COVID-19 who required ICU admission, there was no mutational pattern associated with mortality.

Limitations and strengths of the study

We acknowledge that our study has several limitations. The number of patients included was limited and thus the statistical power may have been too weak to show some between-group differences. Yet, there was no clear trend regarding associations between variant groups/mutations and mortality, suggesting that increasing the number of patients in the cohort would not have changed the results. Changes in management practices occurred during the study period, with more patients infected with variant α (B.1.1.7) and other variant groups receiving dexamethasone, with a possible impact on mortality [19]. Such bias was thus accounted for in the multivariate analysis. Additionally, the period of inclusion of the present study was October 1, 2020, which corresponded in France to the beginning of the second COVID-19 wave, a period when ICU admission policies, ICU patient load and demand, and COVID-19 management strategies were more homogeneous among centres than during the first COVID-19 wave.

Our study also has strengths, including the constitution of a prospective multicenter cohort of well-phenotyped critically ill patients, and the fact that we performed full-length SARS-CoV-2 genome sequencing by means of up-to-date technology.

Conclusions

Patients with pre-existing variants had a different clinical presentation from patients infected with variant α (B.1.1.7) and other variants at ICU admission, characterized by an older age, more comorbidities and a more severe clinical presentation. However, there were no day-28 and day-90 mortality differences between the different groups. We found no association between the variant status or any mutational pattern in SARS-CoV-2 viral genes and mortality.

Abbreviations

ARDS, acute respiratory distress syndrome

ECMO, extracorporeal membrane oxygenation

ICU, intensive care unit

RT-PCR, reverse transcriptase-polymerase chain reaction

SAPS II, simplified acute physiology score

SGTF, S-gene molecular diagnostic assay failure

SOFA, sequential organ failure assessment

VOC, variants of concern

VOI, variants of interest

WHO, World Health Organization

Declarations

Ethics approval and consent to participate: The study was approved by the Comité de Protection des Personnes Nord-Ouest IV (N° EudraCT/ID-RCB : 2020-A03009-30). Informed consent was obtained from all patients or their relatives.

Consent for publication: not applicable

Availability of data and materials: all data generated and analyzed during this study are available on demand.

Competing interests: C.-E. L. has served as consultant for Bayer Healthcare, Carmat and Thermo Fisher Brahms, and received lecture fees from MSD, Aerogen, Advanzpharma and BioMérieux, outside the submitted work. Other authors have no conflict of interest to disclose.

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Tables

Table 1. Characteristics of the 413 patients with severe SARS-CoV-2 infection at the time of intensive care unit admission, according to their infecting SARS-CoV-2 variant.

	Pre-existing variants	Variant α (B.1.1.7)	Other variants	p-values			
	N=183	N=197	N=33	Global comparison	<i>Pre-existing vs. α^a</i>	<i>Pre-existing vs. Others^a</i>	<i>α vs. Others^a</i>
<i>Demographics and comorbidities</i>							
Gender, males	124 (67.8%)	140 (71.1%)	18 (54.5%)	0.165	-	-	-
Age, years	65.0 (± 11.9)	60.5 (± 11.8)	62.2 (± 10.7)	0.001	0.001	0.531	0.823
Diabetes	67 (36.6%)	59 (29.9%)	7 (21.2%)	0.141	-	-	-
Hypertension	108 (59.0%)	98 (49.7%)	16 (48.5%)	0.159	-	-	-
Peripheral vascular disease	28 (15.3%)	19 (9.6%)	1 (3.0%)	0.075	-	-	-
Chronic heart failure	19 (10.4%)	20 (10.2%)	2 (6.1%)	0.851	-	-	-
Chronic kidney disease	34 (18.6%)	23 (11.7%)	1 (3.0%)	0.025	0.178	0.063	0.517
Cirrhosis	3 (1.6%)	4 (2.0%)	0 (0.0%)	1.000	-	-	-
Cancer	15 (8.2%)	8 (4.1%)	1 (3.0%)	0.180	-	-	-
HIV infection	1 (0.5%)	3 (1.5%)	1 (3.0%)	0.274	-	-	-
Corticosteroids	14 (7.7%)	9 (4.6%)	1 (3.0%)	0.445	-	-	-
COPD	21 (11.5%)	8 (4.1%)	2 (6.1%)	0.021	0.021	0.904	0.953
Tobacco	26 (14.2%)	23 (11.7%)	4 (12.1%)	0.769	-	-	-
BMI, kg/m ²	30.2 (± 6.8)	29.8 (± 6.6)	30.2 (± 6.0)	0.857	-	-	-
Clinical frailty scale	3.0 (2.0;4.0)	3.0 (2.0;4.0)	3.0 (2.0;3.0)	0.069	-	-	-
<i>Disease severity upon ICU admission and biological features</i>							
WHO 10-point scale	6 (6;8)	6 (6;8)	6 (6;8)	0.114	-	-	-
SAPS II score	37 (30;50)	30 (24;40)	32 (24;41)	0.000	0.000	0.025	0.971
SOFA score	4 (3;8)	3 (2;4)	4 (2;4)	0.000	0.000	0.156	0.935
Blood neutrophils, G/L	7.9 (5.3;11.3)	6.3 (4.6;9.1)	8.7 (5.8;12.2)	0.006	0.017	0.737	0.061
Blood	0.6	0.7	0.8	0.217	-	-	-

lymphocytes, G/L	(0.4;0.9)	(0.4;0.8)	(0.6;1.0)				
Blood urea level, mM	8.4 (6.0;12.5)	6.5 (4.9;10.2)	6.3 (5.5;8.7)	0.000	0.000	0.038	0.999
D-dimers, ng/mL	1441 (771;2614)	1310 (931;2183)	1300 (799;2030)	0.917	-	-	-
Bacterial coinfection	25 (13.7%)	22 (11.2%)	2 (6.1%)	0.494	-	-	-
<i>Organ supports and management during the first 24 hours^b</i>							
Oxygen	5 (2.7%)	6 (3.0%)	4 (12.1%)	0.045	1.000	0.095	0.114
High flow oxygen	105 (57.4%)	140 (71.1%)	23 (69.7%)	0.017	0.016	0.458	0.998
NIV/C-PAP	55 (30.1%)	51 (25.9%)	12 (36.4%)	0.392	-	-	-
Invasive MV	88 (48.1%)	78 (39.6%)	12 (36.4%)	0.178	-	-	-
Prone position	79 (43.2%)	92 (46.7%)	15 (45.5%)	0.786	-	-	-
ECMO	24 (13.1%)	9 (4.6%)	3 (9.1%)	0.010	0.010	0.989	0.770
ARDS criteria	147 (80.3%)	136 (69.0%)	21 (63.6%)	0.018	0.035	0.098	0.901
Vasopressors	35 (19.1%)	34 (17.3%)	4 (12.1%)	0.654	-	-	-
Antibiotics	123 (67.2%)	115 (58.4%)	19 (57.6%)	0.175	-	-	-

^aPairwise comparisons applying a Sidak correction to account for multiple testing; ^bMore than one type of respiratory support may have been used per patient during the first 24 hours. Thus the total may be more than 100%.

COPD : chronic obstructive pulmonary disease ; BMI : body masse index ; SAPS : simplified acute physiology score ; SOFA : sequential organ failure assessment; NIV: non-invasive ventilation; C-PAP: continuous-positive airway pressure; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; ARDS: acute respiratory distress syndrome

Table 2. Outcomes of the 413 patients with severe SARS-CoV-2 infection during intensive care unit stay, according to their infecting SARS-CoV-2 variant.

	Preexisting variants	Variant α (B.1.1.7)	Other variants	p-values			
	N=183	N=197	N=33	Global comparison	<i>Preexisting vs. α^a</i>	<i>Preexisting vs. others^a</i>	<i>α vs. others^a</i>
Invasive MV	125 (68.3%)	120 (60.9%)	22 (66.7%)	0.312	-	-	-
MV duration, days	16 (9;27)	14 (8;23)	16.5 (10;30)	0.362	-	-	-
ECMO support	29 (15.8%)	19 (9.6%)	6 (18.2%)	0.133	-	-	-
Duration of ECMO, days	17.0 (6.0;31.0)	12.0 (4.0;17.0)	34.5 (8.0;55.0)	0.186	-	-	-
Vasopressor support	87 (47.5%)	94 (47.7%)	17 (51.5%)	0.912	-	-	-
Duration of vasopressors, days	7 (3;15)	9 (4;16)	9 (3;14)	0.862	-	-	-
RRT	47 (25.7%)	53 (26.9%)	7 (21.2%)	0.784	-	-	-
Pulmonary thrombosis	10 (5.5%)	11 (5.6%)	1 (3.0%)	1.000	-	-	-
VAP	88 (48.1%)	85 (43.4%)	15 (45.5%)	0.654	-	-	-
Dexamethasone	143 (78.1%)	168 (85.3%)	31 (93.9%)	0.038	0.199	0.101	0.444
Tocilizumab	6 (3.3%)	25 (12.7%)	4 (12.1%)	0.002	0.003	0.139	1.000
Day-28 mortality	57 (31.1%)	51 (26.2%)	10 (30.3%)	0.550	-	-	-
Day-90 mortality	74 (40.4%)	61 (31.6%)	13 (39.4%)	0.189	-	-	-

^aPairwise comparisons applying a Sidak correction to account for multiple testing.

MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; RRT: renal replacement therapy; VAP: ventilator-acquired pneumonia

Table 3. Relationship between SARS-CoV-2 variants, spike mutations [(substitutions or deletions (Del))] selected a priori and day-28 mortality by multivariate logistic regression analysis.

		All patients	Day-28 survivors	Day-28 non-survivors	ORa ^a (CI95%)	P-value
		N=411	N=293	N=118		
Variants	α	195 (47.4%)	144 (49.1%)	51 (43.2%)	1(ref)	0.347
	Pre-existing variant	183 (44.5%)	126 (43.0%)	57 (48.3%)	0.75 (0.45;1.25)	0.263
	Others	33 (8.0%)	23 (7.8%)	10 (8.5%)	1.31 (0.55;3.13)	0.549
N501Y		220 (53.5%)	162 (55.3%)	58 (49.2%)	1.29 (0.80;2.11)	0.299
N501Y x α^b	None	191 (46.5%)	131 (44.7%)	60 (50.8%)	1(ref)	0.565
	N501Y	25 (6.1%)	18 (6.1%)	7 (5.9%)	1.45 (0.53;3.97)	0.473
	N501Y & α	195 (47.4%)	144 (49.1%)	51 (43.2%)	1.28 (0.77;2.11)	0.342
Del 69-70		193 (47.0%)	143 (48.8%)	50 (42.4%)	1.22 (0.75;1.98)	0.426
Del 140-145		195 (47.4%)	145 (49.5%)	50 (42.4%)	1.20 (0.74;1.95)	0.468
Del 242-244		20 (4.9%)	15 (5.1%)	5 (4.2%)	1.34 (0.44;4.09)	0.607
L5F		16 (3.9%)	11 (3.8%)	5 (4.2%)	1.02 (0.32;3.27)	0.978
L18F		17 (4.1%)	13 (4.4%)	4 (3.4%)	1.19 (0.34;4.10)	0.788
D80A/G		20 (4.9%)	15 (5.1%)	5 (4.2%)	1.21 (0.40;3.66)	0.733
S98F		13 (3.2%)	10 (3.4%)	3 (2.5%)	0.76 (0.18;3.17)	0.703
K417N/T		22 (5.4%)	17 (5.8%)	5 (4.2%)	1.02 (0.34;3.02)	0.976
L452R		8 (1.9%)	5 (1.7%)	3 (2.5%)	1.57 (0.33;7.41)	0.569
S477N		76 (18.5%)	49 (16.7%)	27 (22.9%)	0.79 (0.43;1.45)	0.447
E484K		25 (6.1%)	19 (6.5%)	6 (5.1%)	1.06 (0.38;2.94)	0.908
A570D		192 (46.7%)	142 (48.5%)	50 (42.4%)	1.23 (0.76;2.00)	0.406
D614G		400 (97.3%)	286 (97.6%)	114 (96.6%)	0.65 (0.16;2.68)	0.550
H655Y		6 (1.5%)	4 (1.4%)	2 (1.7%)	1.07 (0.17;6.59)	0.946
P681H		190 (46.2%)	140 (47.8%)	50 (42.4%)	1.29 (0.79;2.09)	0.310
P681R		9 (2.2%)	5 (1.7%)	4 (3.4%)	2.72 (0.61;12.05)	0.189

^aMultivariate analysis adjusted on age, SOFA score at admission, gender and dexamethasone treatment; ^bThis variable comes from the interaction of the variable « variant α » and the variable « N501Y mutation » ; ORa : adjusted odds ratio ; 95% CI : 95% confidence interval

Figures

Figure 1

Time course of emerging SARS-CoV-2 variants during the study period. VOC, variants of concern.

Figure 2

SOFA score and its organ system components in patients with the pre-existing, α (B.1.1.7) or other variants. P values come from ANOVA.

Figure 3

Frequency of preselected SARS-CoV-2 mutations in spike according to day-28 mortality status. There was no statistical difference for any of the comparisons performed (grey bars indicate survivors, black bars indicate decedents).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalTable1.docx](#)
- [AdditionalTable2.docx](#)