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SARS-CoV-2 lineage-dependent temporal phylogenetic distribution and viral load in immunocompromised and immunocompetent individuals

Karen Zafilaza[1*], Antoine Fauchois[1], Valentin Leducq[1], Romain Coppée[2,3], Romane Guilbaud[2], Anna-Maria Franco Yusti[2], Eve Todesco[1], Antoine Bridier-Nahmias[2], Quentin Le Hingrat[2], Sylvain Choquet[4], Patrice Cacoub[5], Zahir Amoura[6], Benoit Barrou[7], Valérie Pourcher[8], Jean-Philippe Spano[9], Martine Louet[10], Laura kramer[11], Tiphaine Goulenok[12], Mathilde Salpin[13], Eric Daugas[14], Richard Dorent[15], Sébastien ottaviani[16], Gérard Zalcman[17], Jade Ghosn[2,18], Charlotte Charpentier[2], Diane Descamps[2], Anne-Geneviève Marcelin[1], Vincent Calvez[1], Valentine Marie Ferre[2], Stéphane Marot[1†] and Cathia Soulie[1†]

Abstract

Objectives Mutational dynamics of SARS-CoV-2 in immunocompromised hosts, although well documented, remain a relatively unexplored mechanism. This study aims to compare the viral replication load and genetic diversity of SARS-CoV-2 in immunocompromised patients and non-immunocompromised individuals (NICs) from two major hospitals in Paris from January 2021 to May 2023.

Methods Cycle threshold (CT) values were measured by TaqPath COVID-19 RT-PCR (Thermo Fisher Scientific). The SARS-CoV-2 whole-genomes from 683 immunocompromised patients and 296 NICs was sequenced using Oxford Nanopore Technologies and used to determine lineage and mutational profile.

Results All immunocompromised patients, but not oncology patients, had lower SARS-CoV-2 viral loads than NICs. The genetic distribution of SARS-CoV-2 was homogeneous between immunocompromised individuals and NICs, with more mutations in immunocompromised patients (IRR = 1,013). Indeed, extensive genomic analysis revealed several mutations specifically associated with immunosuppression status, such as S: T95I, S:N764K, M:Q19E and ORF10:L37F. Conversely, the S: R346K and NSP13:T127N mutations were more common in NICs.

Conclusion Immunocompromised patients have lower viral loads, probably due to their later diagnosis compared to NICs and oncology patients, who have better access to on-site SARS-CoV-2 testing and follow-up. In addition,

†Stéphane Marot and Cathia Soulie are Co-last author.

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*Correspondence:
Karen Zafilaza
karen.zafilaza@aphp.fr

Full list of author information is available at the end of the article

mutational profiles differ between the two groups, with immunocompromised hosts accumulating more mutations compared to NICs.

Keywords SARS-CoV-2, Viral load, Immunocompromised host, Single mutation analysis, Whole-Genome sequencing

Introduction

Over the course of the pandemic, the general population has developed immunity and protection against severe symptoms through vaccination and previous SARS-CoV-2 infections. Immunocompromised individuals remain at an increased risk of experiencing more severe clinical outcomes and higher mortality rates. Several case reports have suggested that immunocompromised patients may shed SARS-CoV-2 for prolonged periods, leading to the accumulation of mutations in the absence of targeted COVID-19 treatment [1, 2]. These mutations can potentially confer resistance to both naturally acquired and vaccine-induced immunity, as well as to monoclonal antibodies, which could eventually lead to the emergence of new variants [3].

Despite growing interest in the role of immunocompromised individuals in viral evolution, a clear understanding of how their infection differ from those of non-immunocompromised individuals is lacking. In particular, it remains uncertain whether prolonged shedding is associated with increased genetic diversity of the virus within the host and whether viral RNA loads differ significantly between these patient populations. In addition, it is not known whether viruses that infect immunocompromised individuals have similar characteristics to those that infect non-immunocompromised individuals. Addressing these gaps is essential to assess the potential risks related in immunocompromised patients and to inform public health strategies.

This study aims to compare the genetic diversity and RNA loads of SARS-CoV-2 between immunocompromised and non-immunocompromised individuals. In particular, we hypothesize that immunocompromised individuals may have higher intra-host genetic diversity and that their RNA load may differ from those of non-immunocompromised individuals from the onset of the infection. By investigating these factors, we aim to provide insights into the SARS-CoV-2 infection in immunocompromised hosts and their potential future role in viral persistence and adaptation.

Methods

Patients

Our retrospective study is based on the Assistance Publique-Hôpitaux de Paris (AP-HP) 'SARS-CoV-2 infection of immunosuppressed patients' (EMERGEN SIID) study (Pitié-Salpêtrière and Bichat-Claude Bernard University Hospitals, France). The design of the work has been approved by the Research Ethics Committee for Infectious and Tropical Diseases (CERMIT; decision number: 2022-05-04). Based on standards currently applied in France individual patient information is not required for internal research.

Immunocompromised patients were selected on the basis of the immunosuppression criteria defined by the French High Council of Public Health (HCSP) on 31 March 2020. The immunocompetent control group consisted mainly of health care workers and patients who did not meet these criteria. The data collection will be carried out continuously from December 2020 to May 2023.

Viral RNA load determination

Viral RNA (80 µL) was extracted from 300 µL of nasopharyngeal samples collected at the time of diagnosis (day 0) using Nuclisens® Easymag® (Biomérieux). Viral RNA load was determined using the TaqPath™ COVID-19 RT-PCR kit (Thermo Fisher). Thermal cycling was performed in a LC480 instrument (Roche) with one cycle of reverse transcription at 53 °C for 10 min followed by a cycle of PCR activation at 95 °C for 2 min and finally 40 amplification cycles each consisting of 95 °C–3 s and 60 °C–30 s. Primers and probes targeting N, ORF1ab and S protein were included in the TaqPath™ COVID-19 Assay multiplex reagents.

Whole -genome sequencing

Whole-genome sequencing of SARS-CoV-2 was performed on samples with a Ct < 28 using an Oxford Nanopore GridION instrument according to a previously established protocol [4]. Sequences with < 90% coverage were excluded.

Statistical analyses

We analyzed SARS-CoV-2 genomes using the Jaccard index to compute distances based on the mutation presence/absence. Multiple correspondence analysis (MCA) visualized the distance matrix, focusing on 167 upstream mutations present in at least 1% of the sequences. The first four principal components captured maximum inertia. A generalized Poisson model assessed the number of mutations per genome, taking into account lineage and group interactions. Chi-squared or Fisher's exact tests with FDR correction identify mutations with significantly different frequencies between immunocompromised and NICs, visualized in a volcano plot. One-way ANOVA analyzes viral load and mutation count by immunosuppression status. Kruskall-Wallis and Dunn's post-hoc tests were performed to determine which

Table 1A Baseline patients' characteristics

	All ***n*** **= 922**	**Immunocompromised patients** ***n*** **= 641**	**Non-immunocompromised control (NICs)** ***n*** **= 281**	***p*-value**
Age, Year, median [IQR]	58.5 [40.0–72.0]	66.0 [51.0–76.0]	40.0 [32.0–54.0]	**< 0.001**
Sex, n (%)				**< 0.001**
Male	439 (48%)	360 (56%)	79 (28%)	
Female	483 (52%)	281 (44%)	202 (72%)	
Lineage– n(%)				**< 0.001**
B.1	12 (1.3%)	7 (1.1%)	5 (1.8%)	-
Alpha	18 (2.0%)	11 (1.7%)	7 (2.5%)	-
Delta	101 (11.0%)	41 (6.4%)	60 (21.4%)	**< 0.001***
Omicron BA.1	228 (24.7%)	185 (28.9%)	43 (15.3%)	**< 0.001***
Omicron BA.2	203 (22.0%)	104 (16.2%)	99 (35.2%)	**< 0.001***
Omicron BA.4/5	135 (14.6%)	109 (17.0%)	26 (9.3%)	**0.003***
BQ.1	122 (13.2%)	99 (15.4%)	23 (8.2%)	**0.004***
XBB	103 (11.2%)	85 (13.3%)	18 (6.4%)	**0.003***
Viral loads, Ct value, median [IQR]		20.6 [18.0–23.0]	19.6 [17.1–22.4]	**0.01**

*Chi-squared test

Table 1B Immunocompromised characteristics and viral loads

	n **(%)**	**CT value, median [IQR]**	**β**	**CI95%**	***p*-value**
Intercept	-	-	20.829	[20.593;21.066]	< 0.001
Solid organ transplant	181 (28.2)	20.5 [18.0–23.0]	-0.186	[-0.523;0.152]	-
Autoimmune or inflammatory diseases	133 (20.7)	21.0 [18.6–23.0]	-	-	-
Oncology	116 (18.1)	19.4 [16.6–21.6]	-1.372	[-1.713;-1.031]	**< 0.001**
Hemato-oncology	82 (12.8)	21.9 [19.1–24.1]	0.743	[0.351;1.136]	-
HIV infection	50 (7.8)	20.1 [18.0–23.0]	0.242	[-0.769;0.285]	-
Anti-CD20 treatment including Rituximab	44 (6.9)	20.8 [18.0-22.3]	0.434	[-0.876;0.008]	-
Intensive care	18 (2.8)	20.2 [18.6–21.8]	0.3	[-0.875;0.276]	-
Respiratory diseases	17 (2.7)	20.5 [18.0–23.0]	-0.163	[-1.007;0.681]	-

One-way ANOVA was used to compare the means of the groups. β is the adjusted effect of the model

immunocompromised group had a higher number of mutations.

Results

Patient's characteristics

A total of 641 hospitalized immunocompromised patients and 281 NICs were enrolled (Table 1A). The NICs were mainly healthcare workers (253/281), but also included patients being treated for conditions not affecting their immune system (28/281). The most common lineage of SARS-CoV-2 infecting immunocompromised patients and NICs was Omicron BA.1 ($n = 185$ [29.0%]) and Omicron BA.2 ($n = 99$ [35.0%]), respectively.

SARS-CoV-2 viral load

We observed that immunocompromised patients had a significantly lower median viral load than NICs on the day of diagnosis (20.72 [17.76–23.18] vs. 19.60 [17.12–22.38], $p = 0.01$).

One-way ANOVA model showed that patients receiving oncologic treatment had a significantly lower viral load compared to other immunosuppression status (Table 1B). This difference is expected to be 1.4 CT lower than other immunosuppression status.

Mutational profile of immunocompromised patients and controls

We identified 167 majority mutations that occur in at least 1% of the individuals included in the study.

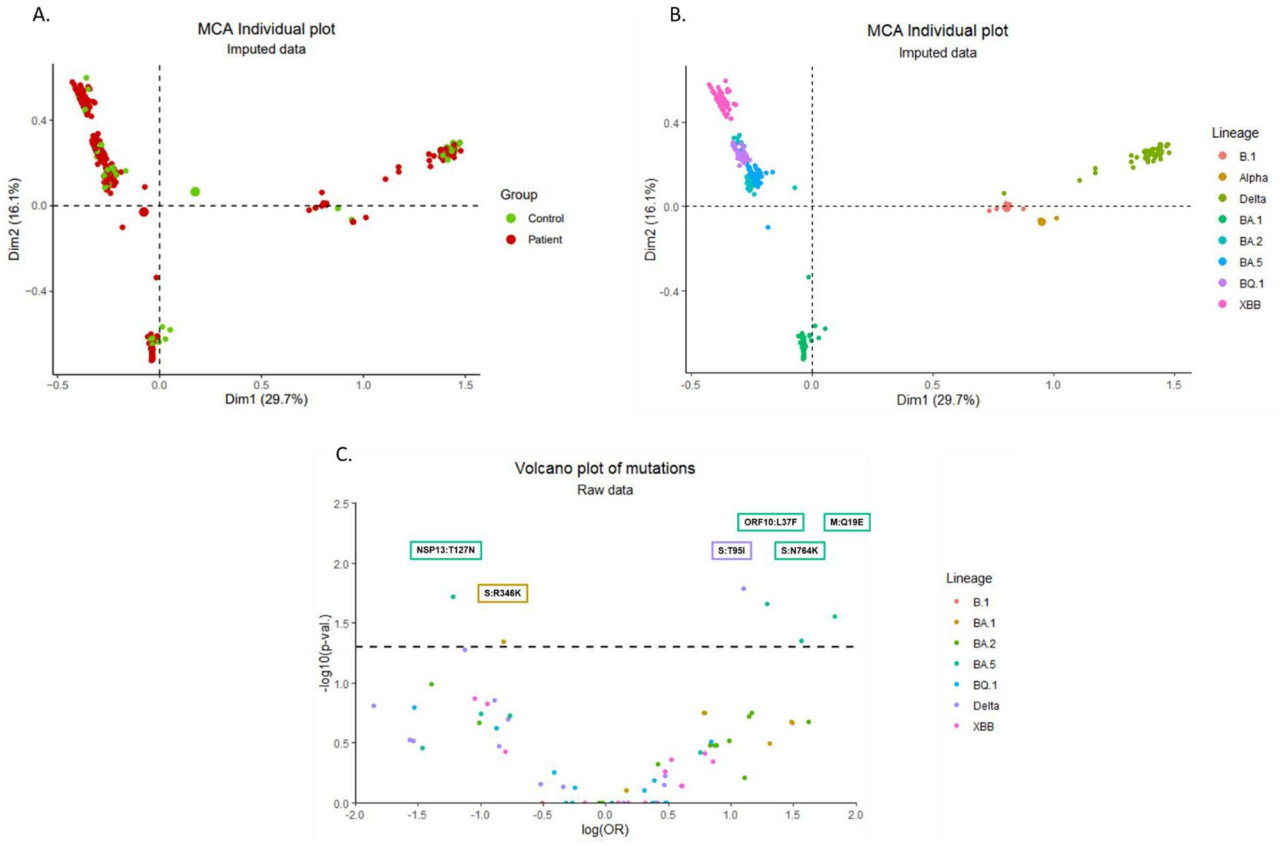

Fig. 1 Whole-genome analysis and single mutation analysis (**A**) Multiple correspondence analysis shows no distinct mutation profile between controls and immunocompromised patients. Sequences form clusters according to their lineage and their similarities from one lineage to another, such as BA.2 and its sub-lineage BA.5 and BQ.1 (**B**). Single mutation analysis display on the volcano plot, showing three amino acid substitutions in the Spike protein and three substitutions in the M, ORF10 and NSP3 proteins. Substitutions S: R346K and NSP3:T127N are positively associated to NICs group and S: T95I, S:N764K, ORF10: L37F and M: Q19E are positively associated to immunocompromised patients group (**C**)

Table 2 Robust generalized Poisson model parameters

Variable	IRR (Incidence Rate Ratio)	CI95%	*p*-value
Group			
Control			
Patient	1.013	[1.013;1.013]	**< 0.001**
Lineage			
Delta	-	-	-
BA.1	1.39	[1.388;1.393]	**< 0.001**
BA.2	1.558	[1.554;1.562]	**< 0.001**
BA.4/BA.5	1.577	[1.568;1.586]	**< 0.001**
BQ.1	1.803	[1.792;1.815]	**< 0.001**
XBB	2.118	[2.077;2.161]	**< 0.001**

Generalized Poisson Model is use to modelized counting variable and the interaction with variable such as group and lineage. Incidence Rate Ration (IRR) demonstrate the effect of group and lineage on the number of mutations on SARS-CoV-2 genome. We removed Alpha and B.1 lineage due to low workforce

Based on the distance matrix, MCA did not reveal a significant difference between the mutational profiles of immunocompromised patients and NICs, as these two groups did not appear to form distinct clusters, regardless of the time period during which they may have been infected and the variant with which they were infected (Fig. 1A). Furthermore, the sequences clustered logically according to the mutational profile of their SARS-CoV-2 lineages, with the exception of lineage BA.2 and its sub-lineages BA.5 and BQ.1, whose viral genomes did not appear genetically distant enough to form distinct clusters (Fig. 1B).

Mutations count study

Based on a robust generalized Poisson model, the modeled mutation count was evaluated as a function of SARS-CoV-2 variant and clade. All clades had a significant effect on mutation count, with the effect increasing as the clade became more recent. Furthermore, being an immunocompromised host was associated with a higher mutation count than controls (IRR = 1.013) (Table 2). To refine our analysis, the group of immunocompromised patients was stratified according to their pathology and differences were observed ($p < 0.001$). Patients admitted to intensivtically different from all other groupse

care were statis (Table 3*)* and had the highest number of mutations *(*Fig. 2).

Single mutation analysis

Focusing on the single mutation level according to lineage and group, 6 amino acid substitutions showed different frequencies between the two study groups. Indeed, the substitutions S: T95I ($p = 0.016$), S: N764K ($p = 0.044$), M: Q19E ($p = 0.028$) and ORF10:L37F ($p = 0.022$) are positively associated with the immunocompromised group, with ORs ranging from 3 to 6 depending on the mutation (Fig. 1C). Among these mutations, S:T95I is associated with anti-CD20 treatment including the rituximab group ($p = 0.002$), while ORF10:L37F is associated with the haemato-oncological group ($p = 0.004$).

Conversely, the NSP3:T127N ($p = 0.019$) and S: R346K ($p = 0.045$) substitutions appeared to be positively associated with the NICs group, with ORs of 0.2 and 0.4 within the immunocompromised group, respectively.

Table 3 Pairwise comparisons of mutations count between patient groups stratified by type of immunosuppression using Dunn's post-hoc test

Comparison	z	W_i	W_j	r_{rb}	*p*	p_{holm}
Autoimmune or inflammatory diseases– Hemato-oncology	1.709	576.206	511.489	0.149	0.088	0.963
Autoimmune or inflammatory diseases - HIV infection	**3.690**	**576.206**	**407.882**	**0.345**	**< 0.001**	**0.005**
Autoimmune or inflammatory diseases - Intensive care	**-3.397**	**576.206**	**807.368**	**0.470**	**< 0.001**	**0.016**
Autoimmune or inflammatory diseases - Control	**5.747**	**576.206**	**410.553**	**0.336**	**< 0.001**	**< 0.001**
Autoimmune or inflammatory diseases - Oncology	0.869	576.206	545.847	0.051	0.385	1.000
Autoimmune or inflammatory diseases - Respiratory disease	0.068	576.206	571.444	0.039	0.946	1.000
Autoimmune or inflammatory diseases - Anti-CD20 treatment including Rituximab	**5.702**	**576.206**	**314.200**	**0.509**	**< 0.001**	**< 0.001**
Autoimmune or inflammatory diseases - Solid organ transplantation	2.619	576.206	494.389	0.190	0.009	0.159
Hemato-oncology - HIV infection	2.123	511.489	407.882	0.230	0.034	0.445
Hemato-oncology - Intensive care	**-4.214**	**511.489**	**807.368**	**0.658**	**< 0.001**	**< 0.001**
Hemato-oncology - Control	3.002	511.489	410.553	0.211	0.003	0.054
Hemato-oncology - Oncology	-0.881	511.489	545.847	0.080	0.378	1.000
Hemato-oncology - Respiratory disease	-0.835	511.489	571.444	0.135	0.404	1.000
Hemato-oncology - Anti-CD20 treatment including Rituximab	**4.018**	**511.489**	**314.200**	**0.438**	**< 0.001**	**0.002**
Hemato-oncology - Solid organ transplantation	0.479	511.489	494.389	0.042	0.632	1.000
HIV infection - Intensive care	**-5.350**	**407.882**	**807.368**	**0.838**	**< 0.001**	**< 0.001**
HIV infection - Control	-0.063	407.882	410.553	0.021	0.949	1.000
HIV infection - Oncology	-2.963	407.882	545.847	0.304	0.003	0.058
HIV infection - Respiratory disease	-2.147	407.882	571.444	0.364	0.032	0.445
HIV infection - Anti-CD20 treatment including Rituximab	1.694	407.882	314.200	0.190	0.090	0.963
HIV infection - Solid organ transplantation	-1.973	407.882	494.389	0.201	0.048	0.582
Intensive care - Control	**6.033**	**807.368**	**410.553**	**0.793**	**< 0.001**	**< 0.001**
Intensive care - Oncology	**3.808**	**807.368**	**545.847**	**0.508**	**< 0.001**	**0.004**
Intensive care - Respiratory disease	2.582	807.368	571.444	0.579	0.010	0.167
Intensive care - Anti-CD20 treatment including Rituximab	**6.587**	**807.368**	**314.200**	**0.952**	**< 0.001**	**< 0.001**
Intensive care - Solid organ transplantation	**4.681**	**807.368**	**494.389**	**0.715**	**< 0.001**	**< 0.001**
Control - Oncology	**-4.466**	**410.553**	**545.847**	**0.278**	**< 0.001**	**< 0.001**
Control - Respiratory disease	-2.385	410.553	571.444	0.327	0.017	0.273
Control - Anti-CD20 treatment including Rituximab	2.267	410.553	314.200	0.208	0.023	0.351
Control - Solid organ transplantation	**-3.234**	**410.553**	**494.389**	**0.180**	**0.001**	**0.026**
Oncology - Respiratory disease	-0.364	545.847	571.444	0.056	0.716	1.000
Oncology - Anti-CD20 treatment including Rituximab	**4.941**	**545.847**	**314.200**	**0.440**	**< 0.001**	**< 0.001**
Oncology - Solid organ transplantation	1.579	545.847	494.389	0.102	0.114	1.000
Respiratory disease - Anti-CD20 treatment including Rituximab	**3.369**	**571.444**	**314.200**	**0.530**	**< 0.001**	**0.017**
Respiratory disease - Solid organ transplantation	1.124	571.444	494.389	0.189	0.261	1.000
Anti-CD20 treatment including Rituximab - Solid organ transplantation	**-4.078**	**314.200**	**494.389**	**0.408**	**< 0.001**	**0.001**

The table summarizes the results of Dunn's post-hoc tests following the Kruskal-Wallis analysis. For each comparison, the z-value, Wilcoxon rank-sum statistics (Wi and Wj), p-value (p) and Bonferroni and holm Bonferroni adjustment (p_{bonf} and p_{holm}) are reported. Significant p-values ($p < 0.05$) are highlighted in bold, indicating statistically significant differences in mutation counts between the compared groups. The results emphasize key differences, such as a higher mutation burden in patients admitted to intensive care compared to most other groups. A negative z-value refers to a lower mutation count for a group compare to the other and a positive z-value refers to an higher mutations count for a group to the other

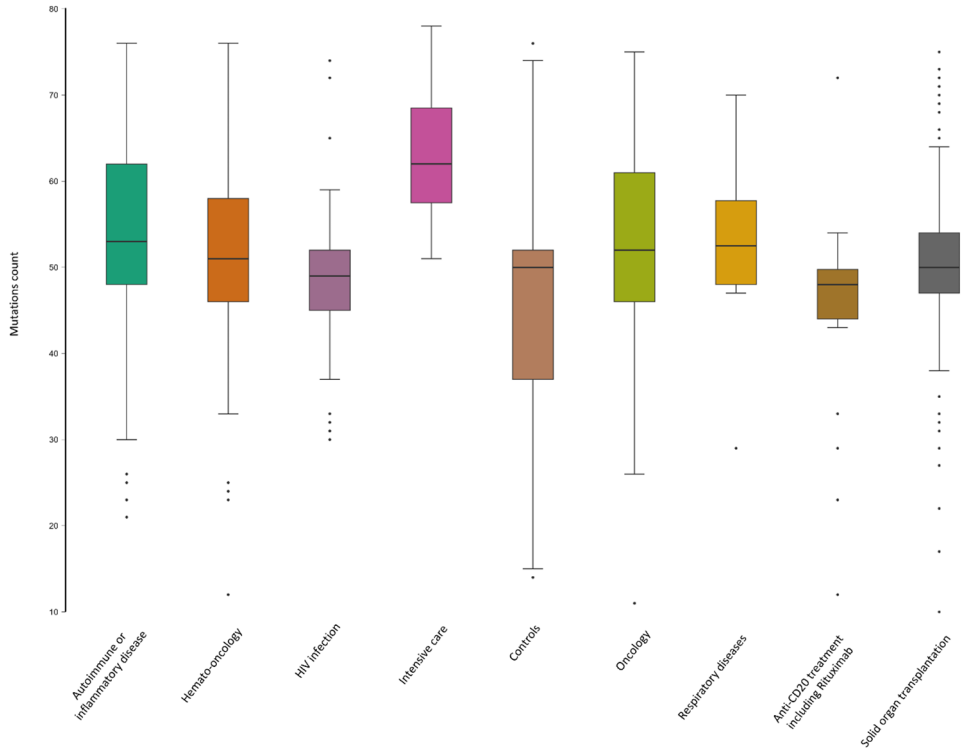

Fig. 2 Boxplot comparing the number of mutations at diagnosis across different patient groups stratified by immunosuppression type. The groups include patients with autoimmune or inflammatory diseases, hematological oncology, HIV infection, intensive care admission, oncology, respiratory diseases, treatment with rituximab, and solid organ transplantation, as well as controls. The boxplots represent the median, interquartile range (IQR), and the range of observed values, with outliers shown as individual points. Notably, patients admitted to intensive care exhibit a higher number of mutations compared to most other groups, while controls have a lower average mutation count

Discussion

In this study, we compared the SARS-CoV-2 genetic diversity and viral load in 683 immunocompromised patients and 296 NICs. The results showed a lower viral load in immunocompromised patients and the presence of different signature mutations compared to controls.

Counterintuitively, we observed lower SARS-CoV-2 viral loads in immunocompromised patients, with the exception of oncology patients. We hypothesize that the delay between infection and diagnostic testing differs between immunocompromised patients and NICs. Healthcare workers, who were often tested asymptomatically, are likely to have received earlier diagnoses, whereas immunocompromised patients were tested at more advanced stages of infection. Oncology patients, who were regularly tested during hospital visits, also had earlier diagnoses. This explains the higher viral loads in NICs and oncology patients.

Whole-genome analysis did not reveal distinct mutational clusters between the controls and the immunocompromised patients, suggesting no significant genetic diversity in SARS-CoV-2 between these populations at the time of diagnosis. However, the higher number of mutations in immunocompromised patients suggests prolonged viral replication prior to hospitalization and testing, leading to mutational accumulation even at the time of delayed hospital testing. In particular, patients admitted to intensive care had a significantly higher number of mutations. This observation may be explained by a possible advanced stage of the disease in these patients, which facilitates the accumulation of mutations [5–7].

Single mutation analysis revealed six mutations that differed between patients and NICs, for which there are no specific data in the literature allowing us to interpret these results, except for the S: T95I and S: R346K mutations. S: R346K was found to be positively associated with Omicron BA.1-infected NICs. This finding is likely due to the 14-day delay in the sampling of BA.1-infected NICs compared to BA.1-infected patients. Indeed, during this period we observed a rapid evolution from BA.1 to BA.1.1 carrying this particular substitution.

In our study, S:T95I showed a higher frequency in Delta-infected immunocompromised patients. Located in the NTD domain, S:T95I occurred in 30% of Delta sequences in France and is a signature mutation of the Iota variant, which has emerged in New York City and has shown resistance to multiple monoclonal antibody therapies, but was not circulating in France during the Delta era. S: T95I is also a signature mutation of Omicron BA.1. This suggests that S: T95I may have first emerged

in immunocompromised patients during the Delta wave and then spread to the general population with the emergence of BA.1. As shown in our previous study, immunocompromised patients had a higher rate of minor mutations. Some signature mutations of newer variants were present as minor mutations in viruses infecting immunocompromised patients before they circulated in the global population [8].

Our study has several limitations. Due to its retrospective nature, the study may suffer from sampling bias, as immunocompromised patients were often diagnosed later in their disease course, which may affect viral load comparisons and mutation identification. Indeed, it has been shown that a longer disease course may result in more mutations [5–7]. Clinical outcomes (symptomatic or asymptomatic status at enrollment, the number of COVID-19 vaccine doses received for example), which we were unable to obtain, could have contributed to a broader understanding of the impact of different viral loads and mutational profiles. There was also a gender imbalance in the control group, probably due to the fact that it consisted mainly of nurses, a predominantly female profession. However, the effect of this imbalance is likely to be minimal, as the study focuses on baseline (D0) parameters, where the influence of sex differences in immune response is limited.

Conclusion

Finally, these findings provide valuable reference points for comparing the characteristics of SARS-CoV-2 infection between immunocompetent and immunocompromised individuals. A clearer understanding of these differences will contribute to ongoing discussions regarding infection control measures, treatment strategies, and surveillance of emerging viral variants.

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Author contributions
K.Z., A.F., V.L., E.T., S.M. and C.S. investigated and analyzed the data. K.Z. and C.S. wrote the original manuscript. A.-G.M., V.C. and D.D. conceptualized the study. All authors provided data and reviewed the manuscript.

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Data availability
The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
The design of the work has been approved by the Research Ethics Committee for Infectious and Tropical Diseases (CERMIT; decision number: 2022-05-04). Based on standards currently applied in France individual patient information is not required for internal research.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Service de Virologie, Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[2]Service de Virologie, Université Paris Cité, INSERM, UMR1137, IAME, Hôpital Bichat-Claude Bernard, AP-HP, Paris, France
[3]Laboratoire de Parasitologie-Mycologie, Université de Rouen Normandie, Rouen 7510 ESCAPE, UR, France
[4]Service d'Hématologie Clinique, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[5]Service de Médecine Interne et Immunologie Clinique, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[6]Service de Médecine Interne 2, Centre National de Référence des Histiocytoses, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[7]Service d'Urologie et de Transplantation Rénale, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[8]Service de Maladies infectieuses et Tropicales, AP-HP, Hôpitaux Universitaires Pitié- Salpêtrière, Paris, France
[9]Service d'Oncologie Médicale, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[10]Service de Santé au Travail, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France
[11]Service de Pharmacie, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[12]Service de Médecine Interne, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[13]Service de Pneumologie, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[14]Service de Néphrologie, Université Paris Cité, INSERM U1149, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[15]Service de Cardiologie, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[16]Service de Rhumatologie, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[17]Service d'Oncologie Thoracique, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France
[18]Service de Maladies Infectieuses, AP-HP, Hôpital Bichat– Claude-Bernard, Paris, France

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