Blood Purification

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## Impact of First Wave COVID-19 Crisis on Dialysis Parameters of COVID-Free Hemodialysis Patients: A NephoCare France Longitudinal Retrospective Cohort Study

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## **Keywords**

 $Hemodialysis \cdot COVID-19 \cdot Treatment \ time \cdot KT/V \cdot Body \\ weight$ 

## Abstract

Background: Chronic hemodialysis (HD) patients are at high risk of severe COVID-19 with a high risk of death. The organization of dialysis units to treat chronic HD patients with CO-VID-19 is demanding to prevent virus transmission both in COVID-free patients and the staff. These constraints may have an impact on the dialysis delivery to COVID-free HD patients. We report our experience in French NephroCare (NC) centers. Methods: We report retrospectively dialysis and nutritional indicators among COVID-free prevalent chronic HD patients' cohort treated in French NC units from February 2020 to April 2020. The COVID-free HD patients were split into 2 subgroups for the analysis, Paris region and other regions because the incidence of COVID-19 was different according to the French regions. Results: The Paris region was the most impacted by COVID-19 with 73% of all the contaminations that occurred in French NC units (n = 118). The dialysis frequency was not reduced all over the NC regions. 2,110 COVID-free HD patients were split into 2 subgroups including Paris region (748 patients) and other regions (1,362

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patients). The weekly treatment time decreased significantly in Paris region from February to April (723–696 min [p <0.00001]) but remained stable in the other regions. The processed blood volume, KT/V, and convective volume declined significantly in the Paris region subgroup but not in other regions. The 3-month weight loss significantly increased in the whole group of patients whatever the region from 0.0 to 0.2% between February 2020 and April 2020 (p < 0.00001). Ultrafiltration rate (UFR) and the normalized proteic catabolic rate remained stable all along the period. The stepwise regression analysis identified February serum albumin level and April UFR as negatively associated with 3-month weight loss. Conclusion: HD delivery to COVID-free HD patients was negatively impacted in the Paris region because of the strong constraints on units' organization related to the treatment of COVID-19+ HD patients and with a higher proportion of limited care/self-care units with less staff resources. The 3-month weight loss increase may be related to the suppression of intradialytic snack that impacted mostly the more malnourished patients or patients with lower interdialytic weight gain. These consequences of the COVID-19 crisis on COVIDfree HD patients must be recognized and corrected to prevent further deleterious effects on patients' outcomes.

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### Introduction

Since the beginning of the COVID-19 crisis, several studies have reported SARS-CoV-2 infection among chronic hemodialysis (HD) patients [1–3]. These patients are particularly exposed to COVID-19 as they cannot fully apply lockdown measures because of the needs of their life-supporting therapy, such as the repeated use of transportation to the dialysis unit and mixing with other patients and staff members in the dialysis unit. Clusters may emerge in HD facilities [1]. Managing chronic HD therapy for HD patients infected by the SARS-CoV-2 is challenging. Measures differ among countries. In Japan, every dialysis patients with a positive polymerase chain reaction-test for SARS-CoV-2 was hospitalized [4]. Some teams have organized specific dedicated units treating exclusively suspected and confirmed patients until discharge to protect noninfected patients [3]. However, the situation is more complicated because a large number of HD patients who are infected do not present symptoms as demonstrated by the high prevalence of positive antibodies against the SARS-CoV-2 in 2 dialysis units [5]. This finding highlights the need of a high vigilance on barrier measures. Moreover, to face the risk of COVID-19 and to manage infected HD patients, both medical and caregiver forces are reoriented to specific tasks and constraints. This may have an impact on the quality of dialysis delivered to patients, including those who are not diagnosed with COVID-19. In this study, we report retrospectively the dialysis parameters of a cohort of HD patients not diagnosed with COVID-19 during the period between February 2020 and April 2020 in the French NephroCare (NC) HD facilities. Our goal was to verify if the adequacy of dialysis has been impacted by the CO-VID-19 epidemics.

### Methods

#### Study Design

This is a retrospective and longitudinal cohort study during the period February 2020 to April 2020 (COVID-19 first wave).

### Patients

We have included in the analysis the chronic HD patients present in the NC units in February 2020. In France, 40 HD units (incenter, limited care, and self-care units) are run by NC. Table 1 shows the distribution of the patients according to the dialysis unit status in Paris region and in the other regions. In Paris region, 63% of the patients were treated in limited care/self-care units. In the 6 other regions, only 17% of the patients were treated in this unit categories. In-center units provide dialysis treatment with a mandatory organization of one nurse for 4 patients and 1 care atten**Table 1.** Distribution of dialysis units' categories and patients inNC Paris region and in the other NC regions

	In-center units, <i>n</i>	Limited care/ self-care units, <i>n</i>	In-center patients,* %	Limited care/ self-care patients,* %
Paris region	2	13	37	63
Other regions	10	15	83	17

 $\ast$  At the end of February 2020 after patient selection (see Fig. 1). NC, NephroCare.

dant for 8 patients, as well as continuous presence of the nephrologist. Limited care and self-care units require 1 nurse for 4 patients without care attendant and continuous presence of the nephrologist. Besides this patients/nurse ratio and medical presence, there is no difference in the unit organization regarding dialysis therapy and biocleaning. Last but not least, the national NC COVID-19 crisis team decided at the beginning of the first wave to change the patients/nurse ratio in the sectors managing COVID-19+ patients (2 patients per nurse instead of 4 patients per nurse) and to make mandatory the presence of the nephrologist during all the session. The medical management of NC units is run in partnership with 64 nephrologists (62 with private status and 2 NC employees). The dialysis prescription and dialysis parameters are run on the common software EUCLID 5 connected to the dialysis stations as reported previously [6]. During the study period, the management of COVID-19+ HD patients without the need of intensive care because of respiratory failure was organized at unit level. In the Paris region, most of limited/self-care units participated in the care of COVID-19 patients. In the other regions, COVID-19 + patients were referred to the incenter unit.

The count of COVID-19 diagnosis in patients and staff was filled out on a daily basis at region level during the study period. We have excluded the patients having been diagnosed with CO-VID-19 and the patients from the NC Tassin-Charcot (Lyon area) prescribed long-hour dialysis because these patients have been switched systematically to standard dialysis in March 2020 and April 2020.

## Dialysis and Nutrition Parameters

The monthly session frequency was calculated in non-CO-VID-19 patients present at least once during the months of February, March, and April 2020. The other dialysis quality parameters were assessed among the patients who were present at least for 10 HD sessions in all 3 months of February, March, and April. This selection excludes de facto COVID-free patients who died during the period and incident patients with less of 3 months of dialysis therapy. The dialysis adequacy parameters included the weekly session time, the prescribed session time, the monthly average of Online Clearance Monitoring (OCM) KT/V, effective blood flow, weekly processed blood volume, and the 3-month weight loss that is the percentage change of prescribed target weight calculated on the last 3 months. Monthly serum albumin was assessed using bromocresol green method. The normalized proteic catabolic rate (nPCR) was derived from pre- and post-dialysis urea.



Fig. 1. Patients' flowchart selection.

Statistical Analysis

According to the non-normality of the data, the results are expressed as median and 25–75th percentiles. The data are compared between the 3 months of the study, February, March, and April 2020 using the Friedman test. This analysis included only complete set of data. We have split the patients in 2 subgroups referred as the "Paris region" (Paris area), the most impacted by the CO-VID-19, and the "other regions." The Mann-Whitney test was used to compare the difference in patients' characteristics and weekly treatment time between the 2 subgroups. Stepwise logistic regression has been run to identify parameters associated with reduction of treatment time and the 3-month weight loss. A p value of 0.05 is considered as significant. The analyses have been run on the MedCalc<sup>®</sup> software (https://www.medcalc.org; 2020; MedCalc Software, Ostend, Belgium).

#### Results

## COVID-19 in French NC Centers

Between February and April 2020 (first wave of CO-VID-19), 118 HD patients treated in NC centers were diagnosed with COVID-19. The regions were impacted differently. In NC Ile de France (Paris area), 86 patients (73% of all the NC COVID-19+ HD patients) were infected (8.8% of the HD patients present in that region at the end of February 2020). In Paris region, the limited care and self-care units supported a higher proportion of infected patients (11%) than the in-center units of the same regions (6.5)% In the other regions, the proportion of patients presenting the COVID-19 was 4.2% in NC Rhône-Alpes (14 patients), 3.4% in NC Provence (3 patients), 1.7% in NC Languedoc (11 patients), 0.5% in NC Occitanie (1 patient), and 0.4% in NC Hauts de France and NC Bearn (1 patient each). Opposite to Paris area, in these regions, all contaminated patients were referred to the incenter units or to the proximity hospitals. In NC unit employees and nephrologists, 20 persons were infected, including 4 nephrologists of the Paris area (20% of the whole group of the nephrologists in this area). The mortality in COVID-19+ HD patients was 16.1%. No mortality was registered in the staff and nephrologists.

## COVID-Free HD Patients during the Study Period (First Wave of COVID-19)

3,030 patients received at least 1 dialysis session in the French NC centers in February, March, and April 2020. The patient flowchart selection is displayed in Figure 1. Patients who were diagnosed with COVID-19 (PCR test and/or CT-scan) were excluded (n = 118). Among the remaining CO-VID-free patients (n = 2,912), 452 were excluded because they had been out of the NC unit at least 1 whole month. The remaining 2,460 HD patients were analyzed for monthly sessions' number (see below). The final analysis of the other



**Fig. 2.** Weekly treatment time in February, March, and April 2020 for all chronic HD patients (**a**, 2,110 patients, no missing data), in the Paris region subgroup (**b**, 748 patients, no missing data), and in the other regions' subgroup (**c**, 1,362 patients, no missing data). HD, hemodialysis.

dialysis parameters was run in HD patients with at least 10 sessions in each of the 3 months of the study (n = 2,159 patients). Among them, 49 patients from NC Tassin-Charcot were excluded because of a switch from long-hour ( $\ge 6$  h) to standard HD leaving 2,110 patients for analysis. These pa-

tients' characteristics are reported in Table 2 (median age = 72 [62–81] years; female = 37%; vintage: 36 [16–69] months; body mass index (BMI) = 25.8 [22.4–29.8] kg/m<sup>2</sup>; diabetes = 32%; Charlson score: 2 [2–4]; hemodiafiltration: 56%). In Table 2 are also reported the characteristics of the 2 subgroups (Paris region and other regions) showing that patients in Paris region were younger and with less diabetic patients.

# Monthly Session Frequency in COVID-Free HD Patients

2,460 non-COVID-19 patients were dialyzed in a French NC center at least once in each of the 3 months of the study. The monthly median number of dialysis sessions in February, March, and April 2020 was 12 (12–13), 13 (13–13), and 13 (13–13), respectively. March and April were significantly higher than February (p < 0.00001), explained by the fact that February in 2020 had 1 working day less than the 2 other months (25 and 26 days, respectively). These numbers confirm that no reduction of frequency was prescribed during the period.

# Weekly Treatment Time and Prescribed Session Time in COVID-Free HD Patients

2,110 patients were dialyzed at least 10 sessions each month of the study. The median of weekly treatment time in February, March, and April 2020 was 716 (702-726), 714 (701–724), and 702 (669–720) minutes (*p* < 0.00001; Friedman test; Fig. 2a), respectively. In the subgroups analysis, the weekly treatment times in the Paris region (748 patients, Fig. 2b) were 723 (715-730), 720 (706-726), and 696 (647-715) minutes, respectively, in February, March, and April 2020 (p < 0.00001) whereas the session time prescription remained unchanged from February to April (247 [245–250] min; p = ns). In the other regions group (1,362 patients), the weekly treatment time in February, March, and April 2020, respectively, was at 709 (697-722), 710 (700-721), and 710 (699-722) (Fig. 2c; p = ns) with a constant session time prescription at 240 (240-247) minutes. The weekly treatment time reduction median between February and April was -29(-66 to -2)minutes in Paris region subgroup and 0 (-5 to +4) minutes in the other regions' subgroup (Mann-Whitney test; p < 0.0001). The stepwise logistic regression analysis to identify parameters associated with a reduction of weekly treatment time above 30 min per week found the Paris region subgroup (odds ratio [OR] = 13.0 [9.9–17.0], p <0.0001) as the only factor related with the reduction of treatment time, whereas the vascular access, age, vintage, gender, February BMI and serum albumin, and the Charlson score included in the model were not.

	All patients	Paris region	Other regions
N	2,110	748	1,362
Age, years	72 (62–81)	65.5 (53-74)	75 (66–83)**
Vintage, months	36 (16-69)	39 (17–75)	34 (16–66)*
Charlson score	2 (2-4)	2 (2-2)	2 (1-4)
BMI (Feb 2020)	25.8 (22.4–29.8)	26 (22.8-30.3)	25.6 (22.1-29.5)*
Female, %	36	37	36
Diabetes, %	32	24	36**
Hemodiafiltration, %	56	50	59**

\* *p* < 0.001, \*\* *p* < 0.0001 between Paris and other regions, patients. HD, hemodialysis; BMI, body mass index.

Table 3. Dialysis parameters in HD COVID-free patients in the whole group and region subgroups

	All patients	Paris region	Other regions
Effective blood flow, mL/min	$n = 2,110^{\circ}$	$n = 748^{\circ}$	$n = 1,362^{\$}$
Mar 2020	348 (333–369)	349 (341–369)	346 (326-373)
Apr 2020	347 (332–369)	348 (337–365)**	346 (326–375)
Weekly processed blood volume, L	$n = 2,110^{\circ}$	$n = 748^{\circ}$	$n = 1,362^{\circ}$
Feb 2020	248 (229–265)	252 (239–266)	245 (223–264)
Mar 2020	247 (231–263)	251 (249–264)	245 (225–263)
Apr 2020	244 (224-258)****	240 (220-252)****	245 (226-264)
OCM KT/V	$n = 2,110^{\circ}$	$n = 748^{\circ}$	$n = 1,362^{\circ}$
Feb 2020	1.7 (1.5–2.0)	1.7 (1.5–1.9)	1.7 (1.4–2.0)
Mar 2020	1.7 (1.4–1.9)	1.7 (1.5–1.9)	1.7 (1.4–1.9)
Apr 2020	1.6 (1.4–1.9)****	1.6 (1.4–1.8)****	1.7 (1.4–2.0)*
Convective volume per session, L	$n = 1,174^{\circ}$	<i>n</i> = 376	n = 798
Feb 2020	26.3 (23.7-28.8)	27.0 (24.6-29.3)	25.9 (23.2-28.6)
Mar 2020	25.7 (23.2-28.5)	26.1 (23.4-28.7)	25.5 (23.0-28.4)
Apr 2020	25.6 (22.1-28.4)****	23.8 (20.1–27.1)****	26.2 (23.5-28.6)***

OCM, online clearance monitoring; HD, hemodialysis. \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.0001; \*\*\*\* p < 0.00001 between months. <sup>§</sup> No missing data.

## Other Dialysis and Metabolic Parameters

The effective blood flow, the processed blood volume per session, the OCM KT/V, the convective volume in patients under hemodiafiltration are presented in Table 3 among the 2 subgroups. All the parameters decreased significantly in the Paris region but not in the other regions' subgroup. We did not find any change during the study period regarding monthly midweek predialysis serum potassium, phosphate, and bicarbonates levels, hemoglobin and erythropoiesis-stimulating agent consumption (data not shown).

# *Three-month Body Weight Loss, Nutritional Parameters, and Inflammation*

In the whole group of COVID-free HD patients, the median of 3-month body weight loss (%) in February, March, and April 2020 was, respectively, at 0.0 (-1.0 to 0.8), 0.0 (-0.9 to 1.1), and 0.2 (-0.7 to 1.4) (Fig. 3; p < 0.00001). Albuminemia median increased significantly between February and April 2020, respectively at 38 (35–41), 38 (35–41), and 39 (36–41) g/L (p < 0.00001). The nPCR did not change significantly along the 3 months and the CRP median was slightly lower in April than February and March (5.0, 4.7, and 4.2 mg/L, respectively; p = 0.006). The



**Fig. 3.** Three-month body weight loss in percent calculated for February, March, and April 2020 in all the chronic HD patients (2,110 patients, one missing case). HD, hemodialysis.

ultrafiltration rate (UFR) median was not different between February 2020 and April 2020 at 8.3 mL/h/kg (p =ns). The stepwise logistic regression analysis in the whole population identified February serum albumin (OR = 0.69 [0.57–0.83]) and April UFR (OR = 0.94 [0.91–0.97]) as significantly associated with the 3-month weight loss. Vascular access, age, vintage, gender, February BMI, and serum albumin, the region (Paris region or other region), the weekly treatment time, OCM, convective volume deltas between February and April, and the Charlson score included in the model were not. In the Paris region with a strong impact of the COVID-19 crisis on dialysis parameters, the weight loss was significantly and negatively associated with the BMI in February (instead of February albuminemia in the whole group) and the UFR in April, but not with the deltas between April and February for weekly treatment time, OCM, and convective volume.

### Discussion

In this retrospective analysis, we report that the CO-VID-19 crisis has had a potential impact on the quality of the dialysis therapy delivery even in COVID-free HD patient. To our knowledge, it is the first report providing this type of data. There are 2 main findings in our study. First, the treatment time and consequently other HD quality indicators have been significantly reduced in CO-VID-free HD patients in the Paris region were the CO-VID-19 pandemic has been at its maximum between mid-March and end of April 2020 with diagnosis of infected HD patients in 8.8% of the entire NC HD population of this region. The pressure of COVID-19 has been much lower in the other regions in which no significant changes on dialysis parameters were found. Second, we observed a decline of the prescribed body weight in April 2020, calculated from the last 3 months. This highlights a significant nutritional impact of the pandemic on CO-VID-free HD patients.

In our experience, no reduction of session frequency was applied in the French NC units. Frequency reduction has been proposed to reduce the patient exposure to potential SARS-CoV-2 contamination with the risk of underdialysis if prolonged [7–9]. The reduction of HD weekly treatment time in Paris region subgroup was not related to the medical prescription that remained unchanged between February 2020 and April 2020. It is explained by organization constraints during the period. The pandemic crisis management has implemented a number of measures that might have impacted the dialysis session duration: First, triage at the dialysis unit entrance might have delayed the patient access to the unit because of the temperature check, the questioning regarding COVID-19 symptoms and way of transportation, the hands frictions with hydroalcoholic solution. However, these measures have been implemented in the NC units all over the country, whatever their status (in-center, limited care, and selfcare units) or the COVID-19 incidence. So, these timeconsuming constraints were present both in the Paris region and in other regions' subgroups ruling out their responsibility in the reduced dialysis delivery. Second, the constraints of the staff protection equipment and of biocleaning were more important in the Paris region than in the other regions because of the number of COVID-19+ HD patients that were treated in dedicated COVID-19 rooms or sectors, mobilizing more resources than in usual times. Also, and as reported above, the proportion of contaminated patients in Paris area was higher in limited care and self-care units. These units have fewer members of staff (no mandatory care attendants opposite to in-center units). This might have contributed to reduced time delivery because of the care organization constraints when contaminated patients were dialyzed in these units. Third, only 7 members of NC staff were diagnosed with COVID-19 in the Paris area during the first wave, that is <1 per unit for 2 months. This cannot have significantly impacted the dialysis delivery. Moreover, the organization of private nephrologists in Paris area was efficient enough to face absenteeism because of COVID-19 contaminations among them (20%). Medical care continuity was preserved all

along this wave. Fourth, the weekly treatment time median in the Paris region subgroup in February 2020 was significantly higher than in the other regions' subgroup (723 vs. 709 min; p < 0.0001). This may have influenced both nephrologists and nurses regarding the decision in cutting the session time for specific care and cleaning.

The 3-month decrease of the target body weight in April 2020 was observed in the whole population of HD patients regardless the regions' subgroups. At the same time, nPCR and UFR did not change significantly during the study period and albuminemia even increased in April 2020. In February 2020 and March 2020, the 3-month weight loss was at 0.0% indicating a stability of the prescribed target weight in the French NC HD patients since at least December 2019. A 0.2% decline may appear marginal. However, the 75th percentile of weight loss was at 1.4%, meaning that 25% of the patients had a spontaneous target body weight loss of 1.0 kilo or above (extrapolated from the median target body weight in February 2020 (71.4 kilos). In 2 months, it is really significant in supposed stable patients. According to the stepwise regression, the level of serum albumin in February (or BMI in February in the Paris region subgroup; both surrogates of a good nutritional status) and the UFR in April 2020 (a surrogate of interdialytic weight gain) were protective of the target weight decrease. It means that patients with markers of protein-energy wasting and low food intake were more exposed to body weight loss during the pandemic confirming the nutritional impact of the COVID-19 crisis in COVID-free HD patients, even in regions with a low COVID-19 incidence. It could be hypothesized that the COVID-19 crisis has triggered anxiety and anorexia in HD patients decreasing the food intake, but the nPCR and UFR did not differ significantly between February 2020 and April 2020 showing that the food intake remained stable. Also, we did not find a relationship between the dialysis parameters alteration in April and the weight loss, ruling out the responsibility of the treatment time and dialysis efficiency reductions on the nutritional status. Importantly, one of the measures implemented in all NC clinics to limit the risk of cross-infection inside the dialysis unit was to suppress the intradialytic snacks and beverages since the end of February 2020. It was also advised by the Société Francophone de Néphrologie Dialyze Transplantation [10]. The dialysis procedure is known to be a catabolic process inducing a negative protein balance [11]. Using labeled leucine or valine or phenylalanine, the intradialytic protein and muscle catabolism have been confirmed [12–15]. This is related, among others, to the amino-acid losses during the session and to the inflammation triggered by the interaction between the blood and the membrane

[16]. Both intradialytic parenteral nutrition [13], oral supplements [14], or a meal [15] have been found effective to prevent the intradialytic catabolism. Then, the food intake during the session is critical for the nutritional balance in HD patients, and its suppression may have impaired the HD patient protein and muscle metabolism. The stability of the nPCR despite this suppression is not a surprise as the impact of the intradialytic snack on nPCR value is expected to be negligible. The snack is only a small share of the whole food intake between 2 sessions (≈6 meals). Moreover, the absence of concomitant decline of serum albumin level may be explained because it is not a direct marker of body composition and because, opposite to inflammation, its decline because of nutrition matters occurs on a long run. Also, we report even an increase in serum albumin in April 2020, parallel to the significant decline in CRP, supporting the hypothesis of reduced inflammation triggered by COVID-19 protective measures (such as generalized masking and extensive use of hydroalcoholic solutions) all over the units. Also, a better fluid management during the period could be proposed as a hypothesis for the increase of serum albumin in April 2020 but we lack objective data on this topic. Blood pressure did not change (data not shown) and we miss bioimpedance measurements because the systematic assessment of fluid status was also suppressed during the study period to limit the risk of crossinfection during the dialysis session.

The strengths of that study are its multicentric aspect, the large population of studied HD patients, and the realtime collection of the dialysis parameters from connected dialysis machine with common software all over the NC organization. On the opposite, the retrospective design is a strong limitation. However, the large number of patients and the connected dialysis machine with online data collection, as stated above, limits this bias. Moreover, the absence of availability of antibodies against the SARS-CoV-2 to clearly sort patients with and without the CO-VID-19 is an important flaw. It is possible that some patients were erroneously classified as COVID-free whereas they had been infected because HD patients may remain asymptomatic [17] or present with unusual symptoms [2]. However, it does not appear as a significant issue regarding the dialysis delivery, as in our opinion the impact of COVID-19 was related to organization constraints. It can be more problematic for the nutritional impact but the constant and even the lower CRP does not feed the hypothesis of a significant number of misclassified CO-VID-19+ HD patients. Last but not least, the absence of routine bioimpedance measurements appears a real weakness as we found a significant weight loss and we are

then unable to provide more precise data on both hydration status and body composition to analyze more objectively this finding in the cohort.

## Conclusion

The pandemic crisis that our country has faced at its peak in March 2020 and April 2020 has significantly impacted the quality of dialysis delivery in COVID-free patients in the Paris area in which the incidence of CO-VID-19 was the highest in French NC units than the other less affected NC regions. In case of a second wave, we must be aware of these findings to avoid in COVID-free patients underdialysis and more serious metabolic complications we did not observe. This may incite us to rethink the protective measures and the resources needed to deliver adequate dialysis therapy in this type of crisis. Moreover, the nutritional status of the patient must remain under strict scrutiny to avoid protein-energy wasting. Alternatives to intradialytic snack, such as proteinenriched oral supplements must be implemented defining the adequate way and moment of its administration to maintain the barrier measures (avoiding mask removal) and deliver it optimally on a nutrition point of view.

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## **Statement of Ethics**

All the patients have signed a written informed consent at admission in NC centers to allow the use of their medical data to support clinical research. This consent has been updated according to the 2018 General Data Protection Regulation for patients who had been admitted before May 25, 2018. According to the French regulation, the manuscript is exempt from Ethical Committee approval because it is a noninterventional study.

#### **Conflict of Interest Statement**

The authors have no conflict of interest to declare in relationship with this study.

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## **Author Contributions**

C.C. contributed to conception and drafting of the work. L.W., H.H., G.J., S.D., M.L., and D.A. contributed to interpretation of data and text revision. S.S. contributed to authorization and supervision of data collection.

#### **Data Availability Statement**

All research data are available and can be accessed via the corresponding author.

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