Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

COVID-19 infection in patients on long-term home parenteral nutrition for chronic intestinal failure☆

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SUMMARY

Background and aims: To investigate the incidence and the severity of COVID-19 infection in patients enrolled in the database for home parenteral nutrition (HPN) for chronic intestinal failure (CIF) of the European Society for Clinical Nutrition and Metabolism (ESPEN).
Methods: Period of observation: March 1st, 2020 March 1st, 2021. Inclusion criteria: patients included in the database since 2015 and still receiving HPN on March 1st, 2020 as well as new patients included in the database during the period of observation. Data related to the previous 12 months and recorded on March 1st 2021: 1) occurrence of COVID-19 infection since the beginning of the pandemic (yes, no, unknown); 2) infection severity (asymptomatic; mild, no-hospitalization; moderate, hospitalization no-ICU; severe, hospitalization in ICU); 3) vaccinated against COVID-19 (yes, no, unknown); 4) patient outcome on March 1st 2021: still on HPN, weaned off HPN, deceased, lost to follow up.
Results: Sixty-eight centres from 23 countries included 4680 patients. Data on COVID-19 were available for 55.1% of patients. The cumulative incidence of infection was 9.6% in the total group and ranged from 0% to 21.9% in the cohorts of individual countries. Infection severity was reported as: asymptomatic 26.7%, mild 32.0%, moderate 36.0%, severe 5.3%. Vaccination status was unknown in 62.0% of patients, non-vaccinated 25.2%, vaccinated 12.8%. Patient outcome was reported as: still on HPN 78.6%, weaned off HPN 10.6%, deceased 9.7%, lost to follow up 1.1%. A higher incidence of infection ($p = 0.04$), greater severity of infection ($p < 0.001$) and a lower vaccination percentage ($p = 0.01$) were observed in deceased patients. In COVID-19 infected patients, deaths due to infection accounted for 42.8% of total deaths.

Conclusions: In patients on HPN for CIF, the incidence of COVID-19 infection differed greatly among countries. Although the majority of cases were reported to be asymptomatic or have mild symptoms only, COVID-19 was reported to be fatal in a significant proportion of infected patients. Lack of vaccination was associated with a higher risk of death.

1. Introduction

The coronavirus SARS-CoV-2 (COVID-19) has been a challenging worldwide pandemic in recent years [1]. The clinical spectrum of COVID-19 ranges from an asymptomatic infection or mild upper respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome (ARDS) [1,2]. Older age and the presence of comorbidities, such as diabetes, cardiovascular diseases and obesity, were reported to be risk factors for progression of pulmonary disease as well as for death [3,4]. Patients affected by chronic organ failure are particularly vulnerable subgroups requiring epidemiological investigation to better understand their associated morbidity and mortality risk and to devise prevention and treatment strategies.

In May 2020, a few months after the beginning of the pandemic, the Home Artificial Nutrition and Chronic Intestinal Failure (HAN&CIF) special interest group of the European Society for Clinical Nutrition and Metabolism (ESPEN) carried out a survey of centres looking after patients on home parenteral nutrition (HPN) for Chronic Intestinal Failure (CIF) [5] to assess the impact of the COVID-19 pandemic on patient care [6]. A total of 78 centers from around the world contributed to the survey, representing ≥3500 patient experiences from both adult and pediatric centers; at that time, 53 centres (67.95%) reported to have no known COVID-19 infected patients, 7 (8.97%) centres were aware that some patients had been infected but were unsure of the exact number of cases, while 18 (23.08%) centres reported that a total of 37 patients had been infected with COVID-19 [6].

In 2015, the HAN&CIF group developed an international multicenter research project to develop consensus criteria for the severity of CIF; the study protocol involved annual prospective data collection of HPN-dependent patients using a structured database [7,8]. As part of the project, data collection in 2021 was used to perform an international multicenter survey to investigate the incidence and severity of COVID-19 infection in patients on long-term HPN for CIF.

2. Materials and methods

2.1. Study protocol, patient population and data collection

The ESPEN international multicenter survey for CIF is based on the retrospective analysis of data prospectively recorded during 12-month follow-up periods. The study started on March 1st, 2015, and data collection was performed on March 1st of each subsequent year, analysing data recorded during the previous 12 months for those patients already included in the database and for new patients who started HPN for CIF during the preceding 12 months. Center invitation to participate in the study occurred via representatives of the national Parenteral and Enteral Nutrition (PEN) societies of the ESPEN Council, who were asked to send the study protocol to members of their PEN societies. Both pediatric (≤18-year-old) and adult patients who were dependent on HPN for either benign-CIF or malignant-CIF were included. The term 'malignant-CIF' indicates the presence of active malignant disease [3]. Data were collected in a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database, termed "the CIF Action day" [3,9].

For each patient, the following data were collected at first inclusion in the database (baseline): age and gender; body weight and height; underlying disease and its benign or malignant nature; pathophysiological mechanism of CIF; HPN requirements (duration, number of days of infusion per week, type of parenteral nutrition admixture, intravenous supplementation (IVS) volume and energy for each day of infusion). The pathophysiological mechanisms of IF were classified as short bowel syndrome with end-jejunostomy (SBS-J), with jejuno-colic anastomosis (SBS-JC) or with jejuno-ileal anastomosis and total colon in continuity (SBS-JIC), intestinal dysmotility (dysmotility), intestinal fistulas (fistulas), mechanical obstruction (obstruction) and extensive small bowel mucosal disease (mucosal disease). The severity of CIF was divided into eight categories, based on the type (Fluid and electrolyte alone, FE; parenteral nutrition including macronutrients, PN) and volume of IVS, calculated as daily mean of the total volume infused per week (volume per day of infusion × number of infusions per week/7 (mL/day)): FE1 or PN1, ≤1000 mL; FE2 or PN2, 1001–2000 mL; FE3 or PN3, 2001–3000 mL; FE4 or PN4, >3000 mL [8]. At the end of the 12-month follow-up period, patient outcome was classified as still on HPN, weaned off HPN or deceased. Weaning from HPN equated to stopping IVS. The causes of death were grouped as HPN/IF-related, underlying disease-related and other causes (neither HPN/IF nor underlying disease-related).

For the present study, the period of observation was March 1st, 2020 (baseline) to March 1st 2021 (end of follow-up) and the date of data collection was March 1st 2021. Patients included at baseline were those already in the database still requiring HPN on March 1st, 2020 and new patients who started HPN between March 1st, 2020 and March 1st, 2021. In order to evaluate occurrence and outcomes associated with COVID-19 infection, a section was added to the ESPEN CIF database including three questions:1) had the patient suffered from COVID-19 infection? (answers: yes; no; unknown); 2) if yes, what was the severity of infection? (answers: asymptomatic; mild, no-hospitalization; moderate, with hospitalization not in the intensive care unit; severe, hospitalization in the intensive care unit); 3) has the patient been vaccinated against COVID-19 (answers: yes, no, unknown).

2.2. Ethical statement

The research was based on anonymized information taken from patient records at the time of data collection. The study was conducted with full regard to confidentiality of the individual patient. Ethical committee approval was obtained by the individual HPN centers according to local regulations.

2.3. Statistical analysis

Data are reported as absolute and relative frequencies. The frequency of COVID-19 infection was reported as "cumulative annual

incidence". Pearson chi-square test and Fisher's exact test were used to analyze frequencies where appropriate. All analyses were carried out using Stata v.15.1, and the significance level was set to $p < 0.05$.

3. Results

3.1. Patient cohort

Sixty-eight HPN centers from 23 countries included 4860 patients (Tables 1 and 2).

3.2. COVID-19 infection

COVID-19 infection was reported as known (answer: yes or no) in 2503 (51.5%) patients, unknown in 2039 (42.0%) and was not reported in 318 (6.5%). COVID-19 infection occurred in 241 patients, corresponding to an annual cumulative incidence rate of 9.6% of the 2503 patients for whom the item was known. Among contributing countries, the calculated annual cumulative incidence ranged from 0 (Australia) to 21.9% (Israel) (Supplemental Table 1). Figure 1 shows the incidence of infections in countries that included in the study at least 10 patients with known infection status. The infection rate was 6.1% in children and 10.2% in adults ($p = 0.036$), 10.3% in benign disease and 7.0% in active cancer ($p = 0.032$) and did not differ between sex ($p = 0.891$), mechanisms of CIF ($p = 0.743$) or IVS ($p = 0.170$) categories.

3.3. COVID-19 infection severity

The clinical severity of COVID-19 infection was reported for 172 of the 241 infected patients. Infection was asymptomatic in 26.7%, mild in 32.0%, moderate in 36.0% and severe in 5.3% (Fig. 2). The severity of infection did not differ between sex ($p = 0.864$), age ($p = 0.720$), underlying disease (0.564), mechanism of CIF ($p = 0.603$) and IVS categories ($p = 0.378$).

Table 1
Contributing home parenteral nutrition (HPN) centers and patients with chronic intestinal failure enrolled in the study, grouped by country of origin.

	HPN Centers	Patients	
Country	n	n	%
France	7	887	18.25
Poland	5	806	16.58
Italy	13	675	13.89
USA	2	639	13.15
UK	4	626	12.88
Belgium	3	304	6.26
Israel	2	239	4.92
Denmark	1	145	2.98
Spain	10	128	2.63
Australia	4	82	1.69
Argentina	1	68	1.40
Sweden	1	57	1.17
Germany	1	46	0.95
Croatia	2	32	0.66
Finland	1	32	0.66
Thailand	4	28	0.58
Brazil	1	17	0.35
Bulgaria	1	16	0.33
Hungary	1	15	0.31
Mexico	1	9	0.19
Latvia	1	5	0.10
Malaysia	1	3	0.06
Turkey	1	1	0.02
Total	68	4860	100

Table 2
Patient demographic and clinical characteristics at baseline enrollment on March 1st, 2020.

Patient categories	% of patients
Sex (n. 4860)	
Males	42.0
Females	58.0
Age category (n. 4815)	
Children (≤18 years)	6.1
Adults	93.9
Disease category (n. 4849)	
Benign	79.7
Malignant (presence of active cancer)	20.3
Mechanism of CIF (n. 4182)	
SBS	59.0
Dysmotility	15.2
Obstruction	13.6
Fistulas	7.5
Mucosal Disease	4.7
Underlying disease (n. 4749)	
Cancer	16.9
Crohn's disease	16.4
Mesenteric Ischemia	13.8
CIPO-primary	7.3
Radiation enteritis	3.8
Carcinomatosis	2.8
Other	25.0
IVS category (L/d) (n. 3949)	
FE ≤ 1	4.3
FE 1–2	1.9
FE 2–3	0.3
FE > 3	0.1
Total FE	7.0
PN ≤ 1	22.0
PN 1–2	38.3
PN 2–3	21.3
PN > 3	9.6
Total PN	93.0

Abbreviations: CIF, chronic intestinal failure; SBS, short bowel syndrome; CIPO, chronic intestinal pseudo-obstruction; IVS, intravenous supplementation; FE, fluids and electrolytes; PN, parenteral nutrition.

3.4. Vaccination against COVID-19

COVID-19 vaccination status was reported for 3962 patients as follows: vaccinated 12.8%, not vaccinated 25.2% and unknown 62.0%. The vaccination rate was 2.6% in children and 39.7% in adults ($p < 0.001$), 31.7% in benign disease and 44.9% in malignant disease ($p < 0.001$), 38.3% in SBS-J, 29.7% in SBS-JC, 18.6% in SBS-JIC, 42.4% in fistulas, 21.2% in dysmotility, 14.8% in mechanical occlusion and 25.0% in mucosal disease ($p < 0.001$), and did not differ between sex ($p = 0.248$), mechanisms of CIF ($p = 0.743$) and IVS categories ($p = 0.800$).

3.5. Association between COVID-19 incidence, severity and vaccination status and patient outcome

At the end of the 12-month follow up period, the outcomes of 2454 patients were reported as follows: still on HPN 78.6%, weaned off HPN 10.6%, deceased 9.7%, lost to follow up 1.1%. The infection rate was significantly higher in the deceased and in those lost to follow up ($p = 0.042$), while infection severity was higher in the deceased group ($p < 0.001$) and those still requiring HPN $p = 0.017$) (Table 3).

Twenty-nine patients infected with COVID-19 died, with causes of deaths shown in Table 4. No death was HPN-related. Deaths due to COVID-19 infection accounted for the 42.8% of the 29 deaths occurred in patients who had the infection.

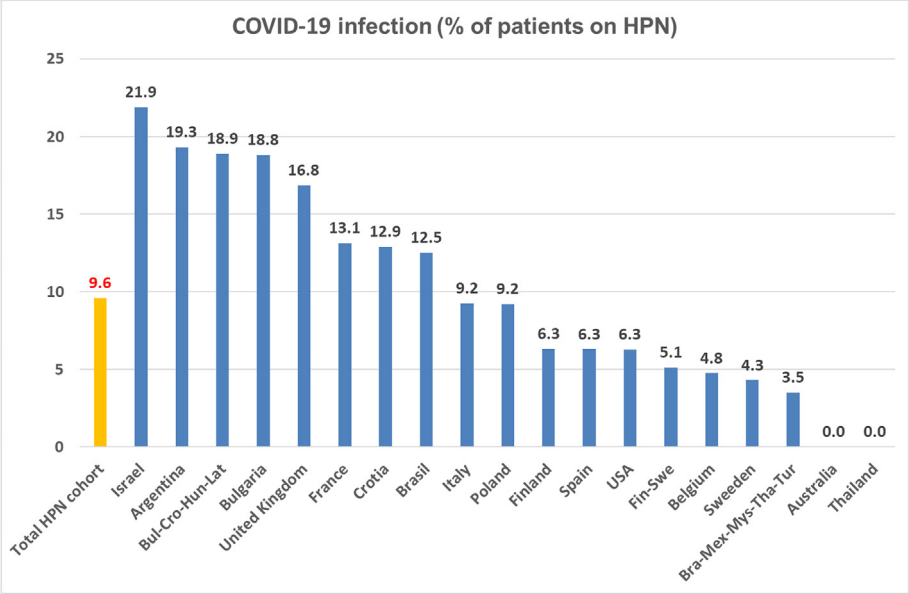

Fig. 1. Annual cumulative incidence of COVID-19 infection in the total cohort of 2503 patients on home parenteral nutrition for chronic intestinal failure and in the cohorts of countries that included in the study at least 10 patients with known infection status.

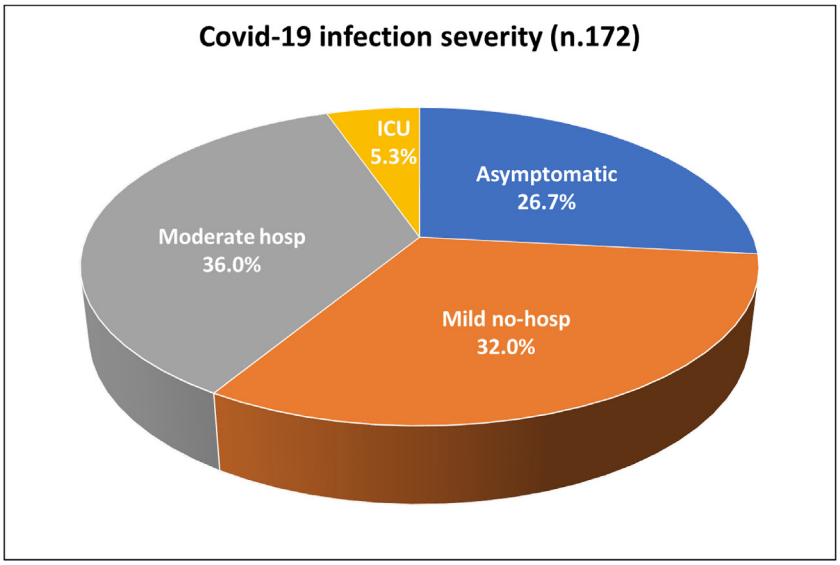

Fig. 2. Percentages of clinical severity of COVID-19 infection in 172 patients on home parenteral nutrition for chronic intestinal failure. Mild, no-hospitalization; Moderate, with hospitalization not in intensive care unit; Severe, hospitalization in intensive care unit.

Table 3
COVID-19 infection incidence, severity of infection, and COVID-19 vaccination in the 12-month outcome categories of patients on home parenteral nutrition (HPN) for chronic intestinal failure.

	COVID-19 infection			COVID-19 infection severity						COVID-19 vaccination		
	n.	Infected n. (%)	p	n.*	Asymptomatic n. (%)	Mild n. (%)	Moderate n. (%)	Severe n. (%)	p	n. **	Vaccinated n. (%)	p
Outcome			0.042						<0.001			0.017
Still on HPN	1930	183 (9.5)		129	38 (29.5)	47 (36.4)	42 (32.6)	2 (1.6)		1376	480 (34.9)	
Weaned off HPN	258	19 (7.4)		15	5 (33.3)	5 (33.3)	5 (33.3)	0		45	10 (22.2)	
Deceased	239	29 (12.1)		20	0	1 (5.0)	12 (60.0)	7 (35.0)		43	8 (18.6)	
Lost to follow-up	27	6 (22.2)		4	2 (50.0)	0	2 (50.0)	0		14	2 (14.3)	

*Number of infected patients for whom the severity of infection was reported.
**Number of patients for whom the vaccination status (yes or no) was known.

Table 4
Causes of death in patients on home parenteral nutrition infected with COVID-19 during the 12-month follow up period.

Death in patients on HPN infected with COVID-19, n.	29
Cause of death, n. (%)	
Not reported	1 (3.4)
Underlying disease-related	14 (48.3)
• Cancer	7
• Cancer + COVID-19	1
• Not reported	6
Other	14 (48.3)
• COVID-19	11
• Intracerebral hemorrage	2
• Renal failure	1

4. Discussion

This study reports the incidence and severity of COVID-19 infection as well as the vaccination status of a large cohort of patients requiring HPN for CIF during the early phase of the pandemic (March 1st, 2020–March 1st, 2021). In the whole group of patients, the annual incidence of COVID-19 infection was 9.7%. By comparison, a recent review of 145 articles, largely based on single-centre experiences in high-income countries, revealed an incidence of COVID-19 among patients on hemodialysis (HD) for chronic kidney disease (CKD) ranging from 0% to 37.6% [9]. Sosa et al. reported a COVID-19 infection incidence rate of 102 per 1000 patients on HD (10.2%) between May 1st to July 31st, 2020, in Guatemala, compared with 3/1000 (0.3%) in the general population [10]. The United States Renal Data System (USRDS) 2021 annual data report showed that, among Medicare beneficiaries in February 2020 undergoing HD, the cumulative incidence of COVID-19 infection by the end of 2020 was 15.8% [11]. The 2022 USRDS report went on to show that patients with CKD had consistently higher COVID-19 testing rates than those without CKD, and rates were higher still for patients undergoing dialysis, suggesting that patients with CKD were consistently more likely to be diagnosed with COVID-19 than those without CKD [12]. We also compared our data with the epidemiological update published by the World Health Organization (WHO) on February 28th, 2021, which reported cumulative cases per 100 thousand population since the beginning of the pandemic [13]. In many countries, the calculated incidence of infection in HPN-dependent patients appeared at least two-fold higher than that in the general population (Fig. 3), suggesting either greater susceptibility and/or risk of exposure to COVID-19 infection and/or a greater rate of testing in patients on HPN for CIF. The incidence of infection was significantly higher in adults than in children and in patients with benign rather than malignant disease. The reasons for these differences are not evident from our data. However, as expected, vaccination rates were higher in patients with cancer and lower in children; it is, of course, possible that both adults and patients with benign disease were at greater risk of exposure to the infection as they spent more time in contact with others outside of their homes. Overall, our data confirm that patients on HPN are a fragile population to be timely protected by repeated vaccination against COVID-19.

COVID-19 infection was asymptomatic or led to only mild symptoms without the need for hospitalization in the majority of cases; notably, these data are comparable to the impact of the disease on the general population observed at the beginning of the pandemic and suggest that HPN-dependence for CIF was not a risk factor for developing more severe clinical features following infection [14,15].

Only 12.8% of patients were reported to be vaccinated at the time of data collection, although this was more frequent in adults, in those with active cancer and for some underlying CIF pathophysiological mechanisms. That said, this low rate of vaccination would, of course, fit with the study's time frame since the first vaccine was approved in December 2020 and therefore only available during the latter two months of the survey, and not in all countries. Furthermore, differences in country policies to prevent COVID-19 infection could have impacted on the incidence rates of both infection and vaccination status. Differences between age categories were due to the initial approval of the vaccine for adults only, while difference between diseases and mechanisms of CIF may have related to vaccine prioritization for those with frailty in some countries.

Both the frequency and severity of COVID-19 infection were greater in the deceased and in those lost to follow up, with

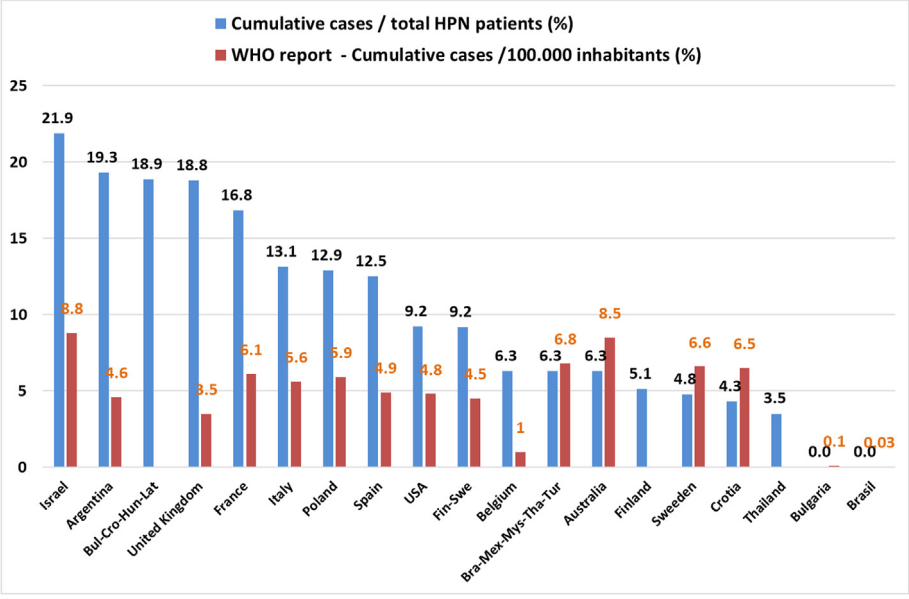

Fig. 3. Cumulative cases of COVID-19 infection in patients on home parenteral nutrition (HPN), from March 1st, 2020 to March 1st, 2021 and cumulative cases per 100 thousand population from the beginning of the pandemic (January 2020) to February 28th, 2021, as reported by the World Health Organization (WHO), in the individual countries.

corresponding low vaccination rates in both latter groups. Moreover, around half of all deaths were due to COVID-19 infection. Again, these data are in keeping with observations in the general population and, of course, serve to highlight the importance of preventative measures, such as mask-wearing and handwashing, physical distancing, and timely vaccination to mitigate infection and its severity [15].

The strength of this study is based on the large patient cohort and its international and multicenter design. However, limitations may include missing data, which likely relate to difficulties encountered in monitoring outpatients, resultant from lockdown restrictions brought into force in virtually all the countries during the follow-up period of the survey. Furthermore, our study design did not investigate the country policies to prevent COVID-19 infection during the period of the data collection, a factor that could have contributed to the differences observed among countries. Nevertheless, the results of this unique study on COVID-19 infection in HPN-dependent patients are in keeping with the impact of the infection on the general population, as well as on patients requiring HD for CKD, which is a useful proxy model of disease.

In conclusion, in patients on HPN for CIF, the incidence of COVID-19 infection differed greatly among countries and was asymptomatic or led to only mild symptoms in the majority of cases but was the cause of death in a consistent number of infected patients. COVID-19 infection, infection severity and lack of vaccination were associated with a higher risk of death. The results highlight the importance of measures to prevent infection.

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Statement of authorship

LP devised the study protocol, collected the data, analyzed the results and drafted the manuscript. The Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN discussed and approved the protocol study, discussed the results and reviewed the manuscript before submission. Coordinators of the participating centers collected the data and reviewed the manuscript upon submission. All authors approved the final version of the manuscript before submission.

Conflict of interest statements

LP: Participation on a Data Safety Monitoring Board or Advisory Board for Takeda, Consulting fees for Takeda, Northsea, NAPO.

SL: Participation on a Data Safety Monitoring Board or Advisory Board for Baxter, Takeda, NorthSea, VectivBio; Grants or contracts from any entity for Baxter, Takeda; Consulting fees for VectivBio, Takeda, Northsea; Support for attending meetings and/or travel for Takeda; Payment or honoraria for lectures for Takeda, Fresenius.

PG: none.

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Appendix A. Supplementary data

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