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ORIGINAL COMMUNICATION

Physical recovery of COVID-19 pneumosepsis intensive care survivors compared with non-COVID pneumosepsis intensive care survivors during post–intensive care hospitalization: The RECOVID retrospective cohort study

Hanneke Pierre Franciscus Xaverius Moonen MD[1,3] | Bert Strookappe PhD[1,2] | Arthur Raymond Hubert van Zanten MDPhD[1,3]

[1] Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, The Netherlands

[2] Department of Physiotherapy, Gelderse Vallei Hospital, Ede, The Netherlands

[3] Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands

Correspondence
Arthur Raymond Hubert van Zanten, MD, PhD, Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP Ede, The Netherlands.
Email: mailto.zantena@zgv.nl

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Abstract

Background: Coronavirusdisease 2019 (COVID-19) pneumosepsis survivors are at a high risk of developing intensive care unit (ICU)–acquired weakness (ICUAW) because of high incidence of acute respiratory distress syndrome and the common need for prolonged invasive ventilation. It remains unknown whether regular postpneumosepsis physical rehabilitation strategies are suitable for this extraordinary patient category.

Methods: We retrospectively compared the physical recovery of COVID-19 and non-COVID pneumosepsis ICU survivors during post-ICU hospitalization, defined as the difference in performance on the Medical Research Council Sum-Score (MRC-SS), Chelsea Critical Care Physical Assessment tool (CPAx), and percentage of predicted handgrip strength (POP-HGS). An analysis of covariance model was built using age, sex, Barthel index, body mass index, admission Acute Physiology And Chronic Health Evaluation II score, adequacy of protein delivery during ICU stay, and ward length of stay as covariates.

Results: Thirty-five COVID-19 ICU patients could be compared with 21 non-COVID pneumosepsis ICU survivors. All patients scored ≤48 on the MRC-SS at ICU discharge, indicating ICUAW. When controlling for covariates, COVID-19 patients performed worse on all physical assessments upon ICU discharge, but had improved more at hospital discharge on the MRC-SS ($\eta^2 = 0.214$, $P = .002$) and CPAx ($\eta^2 = 0.153$, $P = .011$). POP-HGS remained lower in COVID-19 patients throughout hospital stay.

Conclusion: COVID-19 ICU survivors are vulnerable to ICUAW, but they show better tendency towards physical rehabilitation than non-COVID pneumosepsis ICU

survivors during the post-ICU hospitalization period regarding MRC-SS and CPAx. COVID-19 ICU patients might benefit from early, more intensive physical therapy.

KEYWORDS
Covid19, ICU-acquired weakness, pneumonia, recovery, sepsis

CLINICAL RELEVANCY STATEMENT

Coronavirus disease2019 (COVID-19) ICU survivors are at high risk for intensive care unit–acquired weakness, which is well known to have immense personal and societal consequences. As the group of COVID-19 ICU survivors is quickly growing worldwide, insight into their requirements for optimal physical rehabilitation and methods of assessing these is of paramount importance.

BACKGROUND

Intensive care units (ICUs) worldwide have been confronted with a new and distinct form of pneumosepsis: coronavirus disease 2019 (COVID-19) sepsis. The long-term treatment needs of COVID-19 pneumosepsis survivors are not yet fully appreciated, but the development of acute respiratory distress syndrome and the need for prolonged invasive ventilation puts them at a high risk of developing ICU-acquired weakness (ICUAW) and the associated postintensive care syndrome.[1,2] It has been tentatively suggested that this group might benefit from early mobilization and physical exercise strategies, but this is mostly based on experience in related diseases and expert opinion.[3] Results of any randomized controlled trials have not yet been published.

ICUAW is a clinical diagnosis. The Medical Research Council Sum-Score (MRC-SS) and handgrip dynamometry constitute the criterion standard for diagnosis. With MRC-SS, muscle strength is assessed in 12 muscle groups and then individual scores are combined into a sum-score, which yields an overall estimation of motor function. Summed scores below 48 out of 60 and below 36 out of 60 indicate significant and severe weakness, respectively.[4] Handgrip strength (HGS) is measured in kilograms and can be converted to a percentage of predicted (POP) score based on reference values to increase comparability. MRC-SS and (POP) HGS are the most well-known methods for assessment in the ICU population. However, it has been suggested that the lesser-known Chelsea Critical Care Physical Assessment tool (CPAx) might provide benefits, especially in the COVID-19 ICU population, as it is a more holistic measurement tool concerning functional recovery and incorporating respiratory functioning.[5]

In this retrospective cohort study, we aim to compare the (course of) physical functioning of COVID-19 pneumosepsis survivors to non-COVID pneumosepsis survivors at ICU and hospital discharge based on several physical performance scores. Our results may shed light on the optimum method for assessing physical performance in this large group of patients, as well as help to identify the physical therapy approach they will likely require.

METHODS

Study setting and design

We performed a retrospective cohort study in the ICU of the Gelderse Vallei Hospital, a University-affiliated teaching hospital in Ede, the Netherlands.

All ICU patients at our hospital receive standardized early rehabilitation therapy each weekday from ICU admission to hospital discharge. This is a progressive multistep program adapted from the program described by Sommers et al[6] and Schweickert et al,[7] beginning with passive range of motion exercises, followed by (partially) active exercises and progressive mobilization to the edge of the bed or to a chair, standing, and walking. The content of the daily exercise and mobilization regimen as well as the intensity of the applied interventions are adapted to the patient's cardiorespiratory status, level of wakefulness, cooperation, global muscle strength, and tolerance. Exercise and mobilization interventions are progressively continued on the ward upon ICU discharge.

Energy and protein targets in the ICU are calculated by our computerized nutrition protocol based on the Food and Agricultural Organization (FAO) and World Health Organization (WHO) formulae.[8] Protein targets are set according to actual (body mass index [BMI] < 27), corrected (BMI of 27–30; regression to BMI of 27), or ideal body weight (BMI > 30; regression to a BMI of 21 in women and a BMI of 22.5 in men) and amount to 1.5 g/kg/day in a BMI of <30, 2.0 g/kg/day in a BMI of 30–40, or 2.5 g/kg/day in a BMI of ≥ 40. Energy targets are based on calculated resting energy expenditure (REE), with an addition of 20% or 30%, in case of mandatory or spontaneous invasive ventilation, respectively. Targets are adjusted when REE is measured by indirect calorimetry or in case of refeeding syndrome. A progressive feeding strategy towards 100% of targets at admission-day four is used to prevent overfeeding. Actual nutrition and nonnutrition energy and protein delivery are automatically calculated hourly.

Population

Data collected from anonymized records of COVID-19 ICU patients included in the *Bioelectric Impedance Analysis in COVID- 9 positive patients* (BIAC-19) study (Netherlands Trial Register [NTR] NL8562) and the *Resting energy expenditure in mechanically ventilated patients in the ICU and during COnV alescence* (RECOVER-energy ICU) study

(NTR NL8907) were compared with those of a historical cohort of non-COVID pneumosepsis ICU patients, previously collected as part of the RECOVER-energy ICU study and the *Mitochondria Intensive Care* (MIC) study (NTR NL6969). Inclusion and exclusion criteria of these observational trials can be found in the supplementary material. Only patients with polymerase chain reaction–proven COVID-19, or non-COVID pneumosepsis, who had survived the ICU were included in the pooled database to accommodate the research question. Patients transferred from the ICU to a different hospital (COVID-19, n = 5) or discharged to the ward in palliative care (COVID-19, n = 1) were excluded, as physical functioning assessments had not been performed in these cases.

Study parameters

In all prospective studies, physical functioning was assessed with the MRC-SS, CPAx, and measurement of HGS by a trained ICU physiotherapist upon ICU and hospital discharge. An MRC-SS ≤ 48 was considered indicative of ICUAW. HGS was converted to a POP-HGS based on age and sex using a comparable reference population.[9] Other parameters considered were age, sex, BMI, comorbidities (including type 2 diabetes, hypertension, and chronic obstructive pulmonary disease), Barthel index, Acute Physiology And Chronic Health Evaluation (APACHE) II score, Nutrition Risk in Critically Ill (NUTRIC) score, percentage of protein and energy delivered of target during ICU stay, ICU length of stay (ICULOS), hospital length of stay (HLOS), ward length of stay (LOS), duration of mechanical ventilation, and use of neuromuscular blocking agents and immunosuppressive drugs. Steroids were considered if administered continuously or in a singular dose equivalent of ≥100 mg of hydrocortisone. Neuromuscular blocking agents were considered if they were administered continuously for ≥2 h, to exclude anesthetic induction medication.

Statistical analyses

IBM SPSS statistics 27 (IBM Corp, Armonk, NY, USA) was used for all analyses. Continuous values are reported as mean and bias corrected and accelerated bootstrap 95% CI to facilitate comparisons between data with a difference in distribution between the cohorts and to minimize the effect of outliers. Discrete data are presented as numbers (percentages). Normality of the data was visually assessed using the quantile-quantile plot. When inconclusive, the Shapiro-Wilk test was adhered. Differences between groups were assessed using independent samples of *t*-tests for continuous data or chi-squared tests for categorical data. When test assumptions were not met, Mann-Whitney U tests or Fisher's exact tests were used, respectively. An analysis of covariance (ANCOVA) model was built assessing the association between the admission diagnosis (COVID-19 or non-COVID pneumosepsis) and the difference between physical assessment scores upon ICU and hospital discharge. Empirically, age, sex, and ward LOS were added into the model as covariates. In addition, parameters with a significant difference between the means (COVID-19 vs non-COVID patients) were considered. Nonnormally distributed data were transformed (ward LOS) or categorized (Barthel index and BMI). Bias corrected and accelerated bootstrap partial eta-square (η^2) was used to estimate effect size; cut-offs were 0.01, 0.06, and 0.14 for a small, medium, or large effect, respectively. Only two-sided analyses were used. *P*-values <.05 were considered statistically significant. Sensitivity analyses using ICULOS, HLOS, or duration of ventilation as covariates instead of the ward LOS were performed.

Figures representing statistics were made using GraphPad Prism version 8.0.0. for Windows (GraphPad Software, San Diego, CA, USA). The error bars in the figures representing the 95% CI of the mean of the repeated measures on the physical functioning assessment tests on ICU and hospital discharge were adjusted for the between-subject variability.

TABLE 1 Statistical comparison of baseline characteristics

Baseline characteristics	COVID-19 pneumosepsis (n = 35)	Non-COVID pneumosepsis (n = 21)	*P*-value
Age, years (range)	67 (64–70)	63 (57–69)	.16
Sex, male (%)	24 (69)	18 (86)	.2
BMI, mean (range), kg/m^2	29 (28–31)	26 (24–28)	.008*
COPD, n (%)	7 (20)	4 (19)	1
Hypertension, n (%)	9 (26)	6 (29)	1
Diabetes mellitus, n (%)	8 (23)	1 (5)	.13
APACHE II score, mean (range)	15 (13–17)	18 (15–22)	.054*
Barthel index, mean (range)	20 (19–20)	18 (16–20)	.041*
NUTRIC score, mean (range)	3 (3–4)	5 (4–5)	.026*

Note: Continuous values are reported as mean (bias corrected and accelerated bootstrap 95% CI) and discrete data as numbers (percentages). Differences between groups were assessed using independent samples *t*-tests for continuous data or chi-square tests for categorical data. When test assumptions were not met, Mann-Whitney *U* tests or Fisher's exact tests were used, respectively. *P*-values <.05 for statistical comparisons between cohort means were considered statistically significant and are signified with an asterisk *.

Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; NUTRIC, Nutrition Risk in the Critically Ill.

RESULTS

The pooled data set included 35 COVID-19 patients (20 BIAC-19 patients and 15 RECOVER-energy patients) admitted to the ICU between March 2020 and 2021 and 21 non-COVID pneumosepsis ICU patients (19 MIC patients and 2 RECOVER-energy patients) admitted between February 2018 and October 2020. Baseline characteristics and outcome measures are summarized and compared inTable 1 and

TABLE 2 Statistical comparison of outcome and physical functioning of the patients

Outcome measures	COVID-19 pneumosepsis (n = 35)		Non-COVID pneumosepsis (n = 21)		*P*-value
ICU length of stay, mean (range), days	22 (18–26)		18 (12–25)		**.13**
Ward length of stay, mean (range), days	9 (8–11)		9 (6–12)		.17
Hospital length of stay, mean (range), days	32 (26–37)		26 (18–34)		.033*
Duration of invasive mechanical ventilation, mean (range), days	17 (13–21)		12 (6–18)		.19
Duration of neuromuscular blocking agents, mean (range), days	3 (2–4)		1 (0–2)		.001*
Duration of steroid use, mean (range), days	1 (0–1)		1 (1–2)		.17
Protein delivered of target, mean (range), %	78 (92–83)		57 (41–70)		.018*
Energy delivered of target, mean (range), %	75 (67–81)		59 (43–73)		.070
In-hospital mortality, n (%)	0 (0%)		4 (19%)		.016*
28-day mortality, n (%)	0 (0%)		3 (14%)		.048*
Physical functioning scores, mean (range)					
MRC-SS ICU	36 (34–39)		41 (36–46)		.071
MRC-SS hospital	47 (45–50)		45 (39–49)	n = 16	.15
Delta MRC-SS[b]	11 (9–14)		3 (1–6)	n = 16	<.001
CPAx ICU	23 (21–25)		31 (25–36)		.003
CPAx hospital	39 (36–42)	n = 34	40 (35–45)	n = 16	.9
Delta CPAx[b]	16 (14–19)	n = 34	10 (6–13)	n = 16	.005
POP-HGS ICU, %	32 (25–38)	n = 34	48 (35–60)	n = 20	.020
POP-HGS hospital, %	50 (44–57)	n = 34	59 (46–71)	n = 16	.4
Delta POP-HGS[b], %	18 (14–23)	n = 34	12 (8–16)	n = 15	.12

Note: Continuous values are reported as mean (Bias corrected and accelerated bootstrap 95%-confidence interval), discrete data as numbers (%). Differences between groups were assessed using independent samples *t*-tests for continuous data or chi-square tests for categorical data. When test assumptions were not met, Mann-Whitney *U* tests or Fisher's exact tests were used, respectively. *P*-values <.05 for statistical comparisons between cohort means were considered statistically significant and are signified with an asterisk *.

Abbreviations: COVID-19, coronavirus disease 2019; CPAx, Chelsea Critical Care Physical Assessment tool; ICU, intensive care unit; MRC-SS, Medical Research Council Sum-Score; POP-HGS, percentage of predicted handgrip strength.

[a]Number of observations, unless otherwise stated, due to missing data.

[b]Absolute difference between ICU and hospital discharge.

Table 2, respectively. Four (19%) of the non-COVID patients died in the ward, preventing hospital discharge measurements. One COVID patient was not scored on CPAx and HGS upon hospital discharge for reasons unknown.

COVID-19 patients performed worse than non-COVID patients on all assessments—except for POP-HGS, which remained lower throughout hospital stay—upon ICU discharge and better at hospital discharge(Figure 1). All patients scored ≤48 on the MRC-SS at ICU discharge, indicating ICUAW.[2] ICUAW had resolved in more COVID-19 than non-COVID patients upon hospital discharge, although not significantly (17 [49%] vs 4 [25%], *P* =.14).

The association between ICU diagnosis (COVID-19 vs non-COVID) and change (delta) in physical functioning between ICU and hospital discharge was assessed using a univariate linear model (ANCOVA) using age, sex, Barthel index category (normal, 20; reduced, <20), admission APACHE II score, BMI category (normal, 20–24; overweight, 25–29; obese, 30–40), percentage of protein target delivered, and (the square root of) ward LOS as covariates.

The ICU diagnosis was the only covariate with a significant correlation with delta MRC-SS ($F[1, 50] = 5.118$, $P = .002$, partial $\eta^2 = 0.214$) and delta CPAx ($F[1, 49] = 5.496$, $P = .011$, partial $\eta^2 = 0.153$) but not with delta POP-HGS ($F[1, 48] = 0.125$, $P = .6$, partial $\eta^2 = 0.005$). The assumptions for normality of the residuals and equal variances were visually inspected, and they were good.

Separate analyses that used HLOS, ICULOS, or duration of ventilation instead of ward LOS did not challenge the main findings.

DISCUSSION

In accordance with previous research, we observed that COVID-19 ICU patients are prone to ICUAW at ICU and hospital discharge,

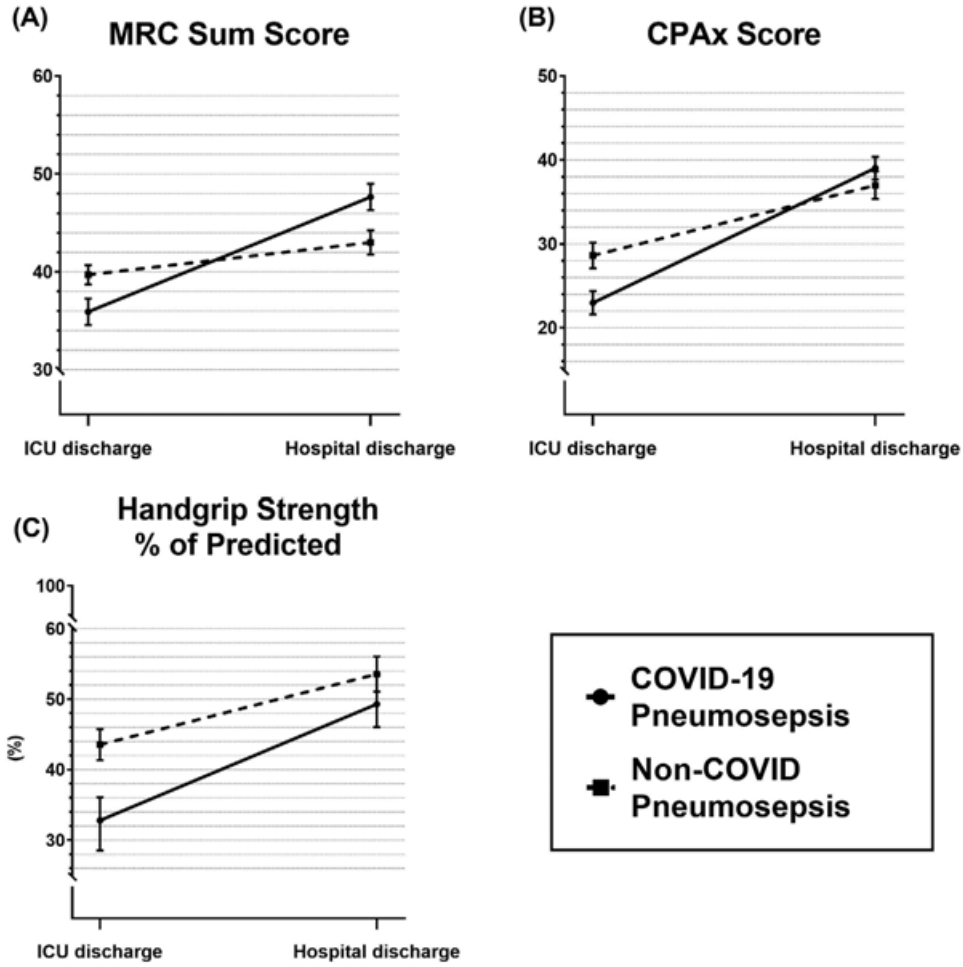

FIGURE 1 Comparison of mean (A) MRC sum scores, (B) CPAx scores, and (C) percentage of predicted handgrip strength measurements for COVID-19 sepsis ICU-survivors and non-COVID pneumosepsis ICU-survivors at ICU and hospital discharge. Error bars representing 95% CI were adjusted for the between-subject variability. COVID-19, coronavirus disease 2019; CPAx, Chelsea Critical Care Physical Assessment tool; ICU, intensive care unit; MRC, Medical Research Council

defined as an MRC-SS of ≤48.[1,10,11] Furthermore, we showed that compared with other pneumosepsis patients, COVID-19 patients scored lower on physical functioning tests upon ICU discharge. Contrastingly, COVID-19 patients showed significantly more improvement of physical functioning on the MRC-SS and the CPAx instruments during post-ICU hospital stay, regardless of baseline characteristics, adequacy of protein administration during ICU stay, and duration of ward LOS. The effect sizes of ICU diagnosis (COVID-19 vs non-COVID pneumosepsis) on delta MRC-SS and delta CPAx, described as partial η^2, were large.

MRC-SS is a well-validated, relatively easy bedside method to establish muscle strength, which is sensitive to identify ICUAW, and reliably predicts hospital mortality, days on a ventilator, ICULOS, and HLOS with excellent interrater reliability.[12–14] In our study, ICUAW resolved in more COVID-19 than non-COVID patients during the post-ICU hospitalization period, although not significantly, likely due to lack of power.

Although the MRC-SS is widely used, it is limited in that it focuses solely on assessment of muscle strength. CPAx was developed as a holistic approach to assessing physical functioning, including respiratory function.[15] The CPAx is an outcome measure designed to assess 10 domains of physical ability in the post-ICU patient: respiratory function, cough, bed mobility, supine to sitting on the edge of the bed, dynamic sitting, sit to stand, standing balance, transferring from bed to chair, stepping, and grip strength. Use of CPAx is not yet ubiquitous; however, it has been translated into several languages and correlates well to other methods such as MRC-SS.[15–19] Taken together, the advantages of CPAx has experts to advocate for its use specifically in the functional assessment of post-ICU COVID-19 patients.[5]

In contrast to the MRC-SS and the CPAx, the change in POP-HGS between ICU and hospital discharge in our study was not different for COVID-19 patients compared with non-COVID pneumosepsis patients. In the past, HGS has been shown to correlate with MRC-SS; however, it has not consistently been shown to predict

outcome across the heterogenic ICU population.[12] This may be due to the lack of discriminatory power of HGS, as a HGS of 0 kg has previously been shown to be associated with acceptable or even normal MRC-SS measurements.[12] In addition, our study may have been underpowered to detect a significant change in HGS.

Limitations and considerations

Our results are subject to the limitations of a retrospective approach. Because of ethical considerations, we were only able to include anonymized records of patients who had previously consented to collection of data in the context of a prospective trial. These trials each had inclusion and exclusion criteria, which may have introduced selection bias into our study. However, our regression model incorporated both empirical covariates and those that differed on baseline between the cohorts. Thus, we assumed that we have minimized any inclusion bias. Nevertheless, our results require the external validation of a prospective design.

To prevent overfitting of the model in a relatively small sample size, we were not able to add all parameters that differed between the cohorts to the eventual model. We chose not to include NUTRIC score, as it incorporates age, comorbidities, and APACHE II scores, which were already considered separately. Furthermore, we did not consider duration of use of neuromuscular blocking agents at this point. However, as duration of use was longer in the COVID-19 cohort, which performed worse upon ICU discharge, and use of neuromuscular blocking agents is associated with increased muscle weakness, inclusion of this parameter in the model likely would not have changed the direction of our results. We collected several parameters reflecting LOS and duration of therapy, which may differ between a COVID-19 and a non-COVID pneumosepsis ICU cohort and independently influence the outcome of physical therapy tests. Because of multicollinearity, we were not able to add all of these as simultaneously covariates in the ANCOVA model. We chose to use ward LOS, as this best reflects the timespan between the repeated measures. Repeating the analyses with ward LOS substituted with any of the other duration parameters did not change the main results and thus omitting the other variables in the main analysis is unlikely to have biased our results. At this point, delivery of macronutrients is only reliably recorded in the ICU at our hospital, and thus we could not report on adequacy of nutrition on the general ward. In future designs, this parameter might be considered if feasible.

We do not routinely measure muscle strength at hospital, nor ICU admission. However, comparing discharge and admission scores would be very insightful in any prospective trials to come.

CONCLUSION

COVID-19 ICU survivors are a vulnerable group concerning ICUAW, but they show better tendency towards physical rehabilitation than non-COVID pneumosepsis ICU survivors during the post-ICU hospitalization period. COVID-19 ICU patients might therefore benefit from early, more intensive physical therapy. Furthermore, the use of the CPAx yielded similar findings as the MRC-SS in our population, and provides theoretical benefits for use in (post-)ICU COVID-19 patients.

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Not applicable.

CONFLICT OF INTERESTS

Arthur Raymond Hubert van Zanten reported having received honoraria for advisory board meetings, lectures, research, and travel expenses from Baxter, Cardinal Health, Danone-Nutricia, DIM-3, Fresenius Kabi, Mermaid, Lyric, and Nestlé-Novartis. The other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Hanneke Pierre Franciscus Xaverius Moonen contributed to the conception of the research, data acquisition, data analysis, and interpretation and writing of the final manuscript. Bert Strookappe contributed to the conception of the research, data acquisition, data interpretation, and revision of the final manuscript. Arthur Raymond Hubert van Zanten contributed to the conception of the research, data interpretation, and revision of the final manuscript.

ETHICS STATEMENT

The ethics committee of Gelderse Vallei Hospital has approved this study. The patients or their legal representatives had previously given informed consent to use all the characteristics and parameters in the context of the BIAC-19, the RECOVER-energy ICU, or the MIC studies. The relevant sections of the respective databases were merged for data analysis. No additional information was gathered. Therefore, we considered the previously obtained informed consent to cover the extended analysis as proposed.

CONSENT FOR PUBLICATION

Not applicable.

ORCID

Arthur Raymond Hubert van Zanten MDPhD https://orcid.org/0000-0001-6276-7192

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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