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# Aerobic exercise capacity in long-term survivors of critical illness: secondary analysis of the post-EPaNIC follow-up study

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## Abstract

**Purpose:** To evaluate aerobic exercise capacity in 5-year intensive care unit (ICU) survivors and to assess the association between severity of organ failure in ICU and exercise capacity up to 5-year follow-up.

**Methods:** Secondary analysis of the EPaNIC follow-up cohort (NCT00512122) including 433 patients screened with cardiopulmonary exercise testing (CPET) between 1 and 5 years following ICU admission. Exercise capacity in 5-year ICU survivors ( $N=361$ ) was referenced to a historic sedentary population and further compared to demographically matched controls ( $N=49$ ). In 5-year ICU survivors performing a maximal CPET (respiratory exchange ratio  $> 1.05$ ,  $N=313$ ), abnormal exercise capacity was defined as peak oxygen consumption ( $VO_{2peak}$ )  $< 85\%$  of predicted peak oxygen consumption ( $\%predVO_{2peak}$ ), based on the historic sedentary population. Exercise limiting factors were identified. To study the association between severity of organ failure, quantified as the maximal Sequential Organ Failure Assessment score during ICU-stay (SOFA-max), and exercise capacity as assessed with  $VO_{2peak}$ , a linear mixed model was built, adjusting for predefined confounders and including all follow-up CPET studies.

**Results:** Exercise capacity was abnormal in 118/313 (37.7%) 5-year survivors versus 1/48 (2.1%) controls with a maximal CPET,  $p < 0.001$ . Aerobic exercise capacity was lower in 5-year survivors than in controls ( $VO_{2peak}$ :  $24.0 \pm 9.7$  ml/min/kg versus  $31.7 \pm 8.4$  ml/min/kg,  $p < 0.001$ ;  $\%predVO_{2peak}$ :  $94\% \pm 31\%$  versus  $123\% \pm 25\%$ ,  $p < 0.001$ ). Muscular limitation frequently contributed to impaired exercise capacity at 5-year [71/118 (60.2%)]. SOFA-max independently associated with  $VO_{2peak}$  throughout follow-up.

**Conclusions:** Critical illness survivors often display abnormal aerobic exercise capacity, frequently involving muscular limitation. Severity of organ failure throughout the ICU stay independently associates with these impairments.

**Keywords:** Exercise testing, Exercise tolerance, Critical illness, Organ failure

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## Introduction

The impact of severe illness requiring admission to an intensive care unit (ICU) extends long beyond the ICU stay. Survivors of critical illness frequently report exercise intolerance and demonstrate reduced strength and six-minute-walk-distance as compared to healthy controls, features paralleled with reduced quality-of-life [1–6]. The post-ICU trajectories of patients may vary strongly [4, 5, 7, 8], but long-term physical impairments have been frequently attributed to illness severity [1, 4, 5]. However, static evaluations of strength and physical function incompletely capture physical fitness, which is a highly dynamic state [9]. Cardiopulmonary exercise testing (CPET) allows assessment of the integrated physiological exercise response, thereby better reflecting peak exercise capacity and functional performance in daily life [10, 11]. CPET, furthermore, allows distinction between cardiorespiratory and muscular impairments primarily limiting exercise [12]. Yet, data on aerobic exercise capacity in ICU survivors are limited to 3 case series, reporting limitations up to 3 months post-ICU [13–15], mainly due to deconditioning and muscle weakness. Evaluation of cardiorespiratory fitness is nonetheless relevant as it informs on long-term prognosis [16–20]. Furthermore, CPET-guided rehabilitation could benefit ICU-survivors, similar to other populations suffering from muscular impairments [21–26], as small increments in exercise capacity entail clinically relevant health benefits [27, 28].

Here, we aimed to investigate cardiorespiratory fitness in long-term survivors of critical illness through CPET. We hypothesized that 5-year survivors of critical illness have impaired aerobic exercise capacity as benchmarked to a sedentary reference population, and further compared to demographically matched healthy controls. We further hypothesized that in these patients, a muscular component frequently contributes to exercise limitation. Finally, we hypothesized that impaired aerobic exercise capacity in ICU survivors independently associates with organ failure severity during critical illness.

## Methods

### Ethics

The protocol of EPaNIC and its long-term follow-up were approved by the Ethical Committee Research UZ/KU Leuven (ML4190). All patients gave informed consent.

### Study design and participants

This is a secondary analysis of the prospective follow-up study of the EPaNIC trial (Clinicaltrials.gov: NCT00512122) in which we included patients assessed for cardiorespiratory fitness by cardiopulmonary exercise testing between 1 and 5 years post-inclusion in

## Take-home message

Critical illness survivors often display abnormal aerobic exercise capacity, frequently involving muscular limitation. Severity of organ failure throughout the ICU stay independently associates with these impairments.

EPaNIC. All long-stayers (ICU stay  $\geq 8$  days), and a random set of short-stayers (ICU stay  $< 8$  days) were invited after 5 years, in the absence of exclusion criteria [29]. A number of patients were additionally invited at intermediate time points according to residual time-slot availability, prioritizing long-stayers. In patients attending the hospital, exercise capacity was assessed with CPET. The primary analysis of this study focused on the prevalence of abnormal exercise capacity in 5-year survivors, referenced to a published historical cohort [30]. Further comparisons were made with CPET results of 49 controls who never stayed in the ICU and who were selected to demographically match the 5-year post-EPaNIC cohort. The secondary analysis examined the association between in-ICU severity of organ failure and exercise capacity from 1 to 5 years post-EPaNIC. See online supplement for further details.

### Cardiopulmonary exercise testing

An incremental, symptom-limited CPET was performed on an electrically braked cycle-ergometer (eBIKE, GE, provided by Acertys). Safety criteria for immediate termination were predefined [12, 31]. The test was performed under continuous monitoring of heart rate, transcutaneous oxygen saturation, and 12-lead electrocardiography. Blood pressure was measured at rest and then every 2 min. Oxygen consumption, carbon dioxide production and minute ventilation were measured on a breath-by-breath basis (JAEGER® Oxycon Pro® and Vyntus CPX® metabolic carts [32], CareFusion). See online supplement for further details.

### Main CPET parameters

The main exercise parameters derived, were obtained at two pivotal points: (1) *peak exercise*, corresponding to the highest work rate achieved and maintained for 30 s; and (2) the *anaerobic threshold*, the point during exercise supposedly marking the onset of anaerobic metabolism [12].

At *peak exercise*, we obtained (a) peak oxygen consumption rate ( $\text{VO}_{2\text{peak}}$ ) as index of cardiorespiratory fitness [12, 18]; (b) peak work rate; (c) peak heart rate ( $\text{HR}_{\text{peak}}$ ), and heart rate reserve (HRR); (d) peak ventilation ( $\text{VE}_{\text{peak}}$ ), and ventilatory reserve, the ratio of  $\text{VE}_{\text{peak}}$  to maximal voluntary ventilation (MVV); (e)

peak oxygen pulse ( $O_2$ -pulse); (f) respiratory exchange ratio (RER), calculated as  $VCO_{2peak}/VO_{2peak}$ .

(g) The *anaerobic threshold* is generally referenced to the  $VO_2$  at which  $CO_2$ -production exceeds  $O_2$ -consumption due to lactic acid buffering ( $VO_{2AT}$ ); (h) additionally, we determined the ratio of ventilation rate to  $CO_2$ -production rate at the anaerobic threshold ( $VE/VCO_{2AT}$ ) or ventilatory efficiency [33].

(i) In addition to estimates at peak exercise and at the anaerobic threshold, the metabolic efficacy for mechanical work, reflected by  $\Delta VO_2/\Delta WR$ , was calculated.

Predicted values were based on reference equations from a historic sedentary benchmark population published by Jones et al. [30]. See online supplement for further details.

### Categorising CPET outcomes

The main goal of the classification of the CPET studies was to identify patients in whom abnormal aerobic exercise capacity was primarily due to peripheral limitations, presumably due to muscular impairments or deconditioning, further referred to as muscular limitations. To avoid erroneous labelling of patients delivering insufficient effort, we first excluded patients with submaximal CPET. Maximal effort was defined as  $RER > 1.05$  [9]. Next, we identified patients with abnormal exercise capacity, defined as  $VO_{2peak} < 85\%$  of predicted  $VO_{2peak}$  [12, 34]. We subsequently identified patients with ventilator and gas exchange limitations and those in whom signs of cardiac disease were present. Patients without a clear indication of such pathological exercise responses were considered to predominantly exhibit muscular limitation. See online supplement for further details.

### Severity of organ failure

Severity of organ dysfunction was quantified as the maximal Sequential Organ Failure Assessment (SOFA-max) score during ICU stay, ranging from 0 to 24, with higher values indicating more severe organ failure [35, 36].

### Other outcomes

At follow-up, patients also underwent pulmonary function testing, evaluation of peripheral and respiratory strength, functional exercise capacity as assessed with the 6-min-walk-distance (6MWD), and quality-of-life assessment with the SF-36 [6, 8]. See online supplement for further details.

### Statistics

The primary outcome was evaluation of exercise capacity and prevalence of abnormal exercise capacity in 5-year survivors, as referenced to a historical sedentary population [30]. Data were further compared with

demographically matched healthy controls. Secondary outcomes included description of exercise limiting factors and the association between the severity of organ dysfunction and exercise capacity in ICU survivors. Descriptive analyses are provided in the online supplement.

### Association between aerobic exercise capacity and severity of organ failure

To assess whether long-term aerobic exercise limitation was independently associated with severity of organ dysfunction throughout follow-up, data from all CPET studies between 1- and 5-year follow-up used and we created an adjusted linear mixed model for  $VO_{2peak}$ . Fixed effects included the SOFA-max, time-to-follow-up in years, the interaction between SOFA-max and time, as well as a priori identified confounders, including: age and BMI at ICU admission, gender, diabetes mellitus at ICU admission, malignancy, preadmission dialysis, randomisation, diagnostic category, sepsis upon admission, and ICU-length-of stay [37]. The correlation within the repeated measures over time was modelled through an unstructured covariance matrix [38, 39]). Details are provided in the online supplement.

### Exploratory analyses

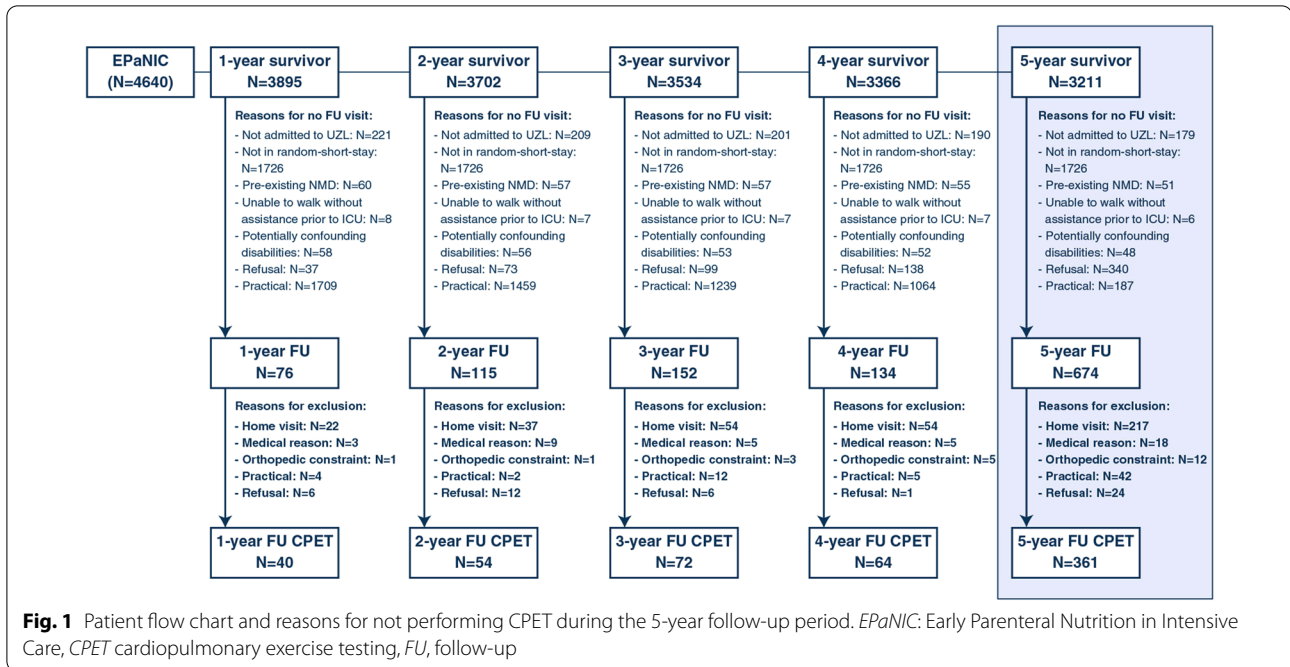
If an independent effect of the severity of organ failure on  $VO_{2peak}$  was demonstrated, we further examined whether the effect of severity of organ failure could be explained by persisting weakness. For this purpose, we built additional linear mixed models in which both knee and hip strength at follow-up were added as covariates in separate models.

Descriptive analyses were conducted with SPSS version 27 (IBM), linear mixed modelling with the MIXED procedure in SAS version 9.4 (SAS institute).

## Results

### Participants

Throughout the 5-year period, 1151 follow-up visits were performed in 774 unique patients. CPET was performed during 591 follow-up visits (40/76 visits at 1-year, 54/115 at 2-year, 72/152 at 3-year, 64/134 at 4-year and 361/674 at 5-year), involving 433 unique patients. Reasons for not performing CPET are provided in Fig. 1. Characteristics of enrolled and non-enrolled 5-year follow-up patients are depicted in Table 1. Follow-up patients who performed a CPET were significantly younger, more frequently were male, had fewer comorbidities, received vasopressors less frequently and for shorter periods of time, less frequently acquired a new infection and had shorter ICU stays as compared to patients who did not perform a CPET. Mean time to follow-up was



5.5 ± 0.2 years. In parallel, 49 controls were tested with similar demographics as the 5-year cohort (Supplementary Table 1). Characteristics of the cohorts at intermediate time points are provided in Supplementary Table 2.

#### Cardiopulmonary exercise capacity in 5-year survivors

At 5 years follow-up, 313/361 (86.7%) patients performed a maximal test, of which 118 (37.7%) revealed impaired aerobic exercise capacity. This was significantly different from controls, in whom 48/49 (98.0%) performed a maximal test, of which 1/48 (2.1%) exhibited abnormal aerobic exercise capacity ( $p < 0.001$ ).  $VO_2$ peak was significantly lower in 5-year follow-up patients as compared to controls ( $VO_2$ peak: 24.0 ± 9.7 ml/min/kg versus 31.7 ± 8.4 ml/min/kg,  $p < 0.001$ ; %pred $VO_2$ peak: 94 ± 31% versus 123% ± 25%,  $p < 0.001$ ) (Fig. 2; Table 2). The anaerobic threshold was identified in 331/361 (92%) patients at 5-year follow-up and values were significantly lower as compared to the healthy controls ( $VO_2$ AT: 15.3 ± 8.7 ml/min/kg versus 18.5 ± 6.0 ml/min/kg,  $p = 0.015$ ; % predicted  $VO_2$ peak: 55% ± 16% versus 71% ± 21%,  $p < 0.001$ ). Other CPET results are shown in Table 2 and Supplementary Table 3.

#### Factors limiting cardiopulmonary exercise capacity in 5-year survivors

In 5-year follow-up patients exhibiting abnormal exercise capacity, the anaerobic threshold was abnormal in 78/118 (66.1%), undetermined in  $N = 4/118$  (3.4%) and normal in 36/118 (30.5%) of patients. After eliminating patients in

whom primary ventilatory [7/118 (5.9%)], gas exchange [5/118 (4.2%)], combined respiratory [3/118 (2.5%)] limitation, or cardiac disease limiting exercise [12/118 (10.2%)] was suspected, a primary muscular limitation was presumed in 71/118 (60.2%) patients (Supplementary Fig. 1). In the single control subject with abnormal  $VO_2$ peak, the anaerobic threshold was normal and there were no signs of ventilatory or gas exchange impairment, nor signs of cardiac ischemia, hence abnormal exercise capacity was likely due to muscular limitation.

#### Other physical outcomes

As reported previously in general ICU survivors, 5-year follow-up patients performed worse on all other outcomes as compared to controls (Table 3) [6]. Patients who received a CPET had higher peripheral and respiratory muscle strength, performed better on pulmonary function tests, 6-MWD and functional quality-of-life, as compared to those who did not perform CPET.

#### Association between severity of organ failure and aerobic exercise capacity

Severity of organ dysfunction significantly and independently associated with  $VO_2$ peak, with a reduction in  $VO_2$ peak of 0.345 ml/min/kg (95% CI – 0.669 to – 0.021,  $p = 0.037$ ) per point increase in SOFA-max throughout follow-up (Supplementary Table 4). This effect did not depend on the timing of evaluation during the 1- to 5-year study period. There was

**Table 1 Admission and ICU-characteristics of patients evaluated at 5-year follow-up**

	CPET (N = 361)	No CPET (N = 313)	p value
<b>Admission</b>			
Age <sup>a</sup>	59 ± 14	68 ± 15	< 0.001
Gender, male	254 (70.4)	196 (62.6)	0.003
BMI <sup>a</sup>	27.5 ± 4.7	26.8 ± 5	0.056
Diabetes mellitus	40 (11.1)	58 (18.6)	0.006
Malignancy	47 (13)	59 (18.9)	0.036
Preadmission dialysis	3 (0.8)	0 (0)	0.253
Diagnostic category			0.131
Cardiac surgery	146 (40.4)	154 (49.4)	
Emergency SICU	164 (45.4)	119 (38.1)	
Elective SICU	26 (7.2)	18 (5.8)	
Medical ICU	25 (6.9)	21 (6.7)	
Randomisation, late PN	181 (50.1)	163 (52.2)	
APACHE II	26 (16–33)	24 (17–34)	0.543
Sepsis upon admission	88 (24.4)	88 (28.2)	0.260
<b>ICU stay</b>			
Mechanical ventilation	351 (97.2)	298 (95.5)	0.231
Duration of mechanical ventilation, days	3 (1–8)	3 (2–9)	0.190
Vasopressors/inotropics	291 (80.6)	269 (86.2)	0.052
Duration of HD support, days	2 (1–5)	3 (2–9)	< 0.001
New infection	110 (30.5)	120 (38.5)	0.029
New dialysis	26 (7.2)	31 (9.9)	0.204
Bilirubin > 3 mg/dL	64 (17.8)	56 (17.9)	0.954
ICU LOS, days <sup>b</sup>	5 (2–12)	7 (3–14)	0.001
ICU-stay > 8 days	136 (37.7)	140 (44.9)	0.058

Continuous variables are depicted as mean (standard deviation)<sup>a</sup> or median (interquartile range)<sup>b</sup>, categorical variables are depicted as number (percentages)

ICU intensive care unit, CPET cardiopulmonary exercise test, BMI body mass index, SICU surgical intensive care unit, PN parenteral nutrition, APACHE II acute physiology and chronic health evaluation, HD hemodynamic, LOS length of stay

no difference between VO<sub>2</sub>peak at intermediate time points and at 5-year follow-up.

### Exploratory analyses

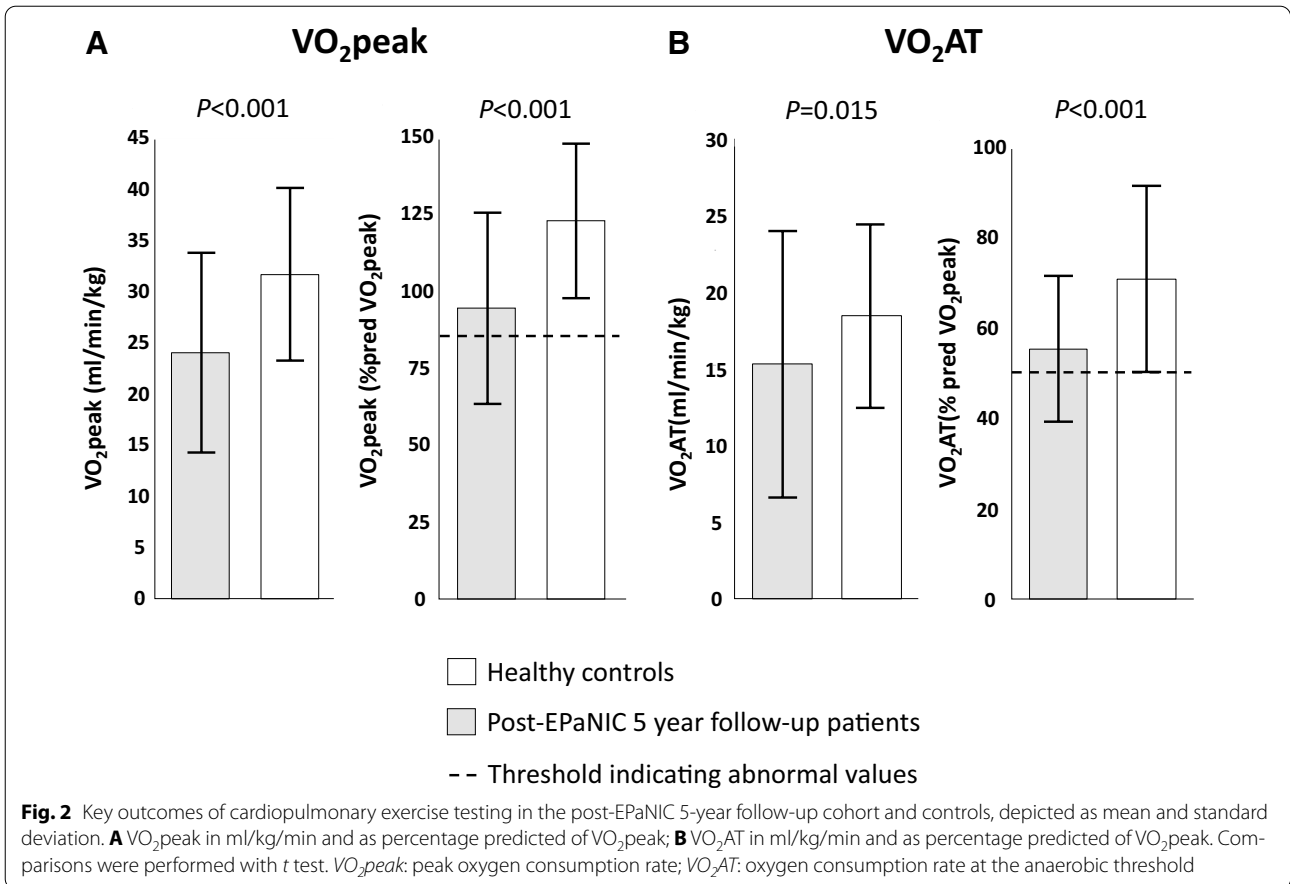
Both knee extensors strength [increase in VO<sub>2</sub>peak of 0.229 ml/min/kg per 10 N increase in strength (95% CI 0.132–0.327, *p* < 0.001)] and hip flexors strength at follow-up [increase in VO<sub>2</sub>peak of 0.182 ml/min/kg per 10 N increase in strength (95% CI 0.071–0.294), *p* = 0.001] independently associated with VO<sub>2</sub>peak at follow-up. In these models adjusting for strength at follow-up, SOFA-max remained independently associated with VO<sub>2</sub>peak. Hence, strength at follow-up did not statistically explain the effect of SOFA-max on VO<sub>2</sub>peak (Supplementary Table 4).

### Discussion

In this cohort of ICU survivors, we evaluated aerobic exercise capacity with cardiopulmonary exercise testing throughout a 5-year follow-up period. Peak oxygen consumption rate and oxygen consumption rate at the anaerobic threshold were lower in 5-year ICU-survivors as compared to demographically matched controls and abnormal exercise capacity was present in 118/313 (37.7%) of patients. Muscular limitation contributed to abnormal exercise capacity in 60.2% of these patients. Adjusted for confounders, the severity of organ failure throughout the ICU stay independently associated with peak oxygen consumption. The association between SOFA max and VO<sub>2</sub>peak was not explained by strength at follow-up.

Though physical impairments after ICU- and hospital discharge and their association with illness severity are well-documented in various subpopulations of critical illness [1, 3, 7], data on aerobic exercise capacity in





ICU survivors are largely uncharted. In a cohort of 50 patients ventilated for at least 5 days, severe exercise limitation with VO<sub>2</sub>peak at 56% ± 16% and an anaerobic threshold of 41% ± 13% of predicted VO<sub>2</sub>peak were described, 24 ± 14 days after hospital discharge [14]. In 10 patients, ventilated for acute lung injury, VO<sub>2</sub>peak was significantly lower 6 weeks following hospital discharge as compared to controls (median 17.8 ml/kg/min versus 31.8 ml/kg/min) [15]. Ong et al. demonstrated reduced VO<sub>2</sub>peak in 18/44 (41%) SARS-survivors, 3 months after hospital discharge, of which 10 had required intensive care [13]. Our study focused on the longer-term exercise limitations and showed overall improved aerobic exercise capacity as compared to results obtained very early after hospital discharge [14, 15]. However, exercise capacity was still reduced as compared to controls, and 37.7% of patients had an abnormal exercise capacity 5 years following ICU stay, although striking variability between patients was observed. Noteworthy, our data show no difference in exercise capacity between intermediate time-points and the 5-year follow-up point, suggesting recovery of exercise capacity may have occurred within the first year following ICU stay.

We further demonstrated an independent association between in-ICU severity of organ dysfunction and VO<sub>2</sub>peak in ICU survivors up to 5 years post-ICU. We chose the SOFA-max score to reflect the severity of organ dysfunction throughout the ICU stay, rather than admission severity scores, which would not capture new organ failure due to complications occurring during ICU stay.

Previous data showed that up to 3 months after hospital discharge, deconditioning and muscular factors frequently limited exercise capacity [13–15]. We demonstrated that, at 5 years, muscular limitation contributed to abnormal exercise capacity in 60.2% of cases. This is consistent with previous reports, indicating neuromuscular sequelae of critical illness up to 5 years post-ICU [3, 6], in particular in patients with intensive care unit acquired weakness (ICUAW) [8]. Furthermore, we here demonstrate that hip and knee strength at follow-up independently associate with exercise capacity. Intriguingly, strength at follow-up did not statistically explain the impact of severity of organ failure, an important risk factor for the development of ICUAW [40–45]—and hence for the functional legacy of critical illness—on exercise capacity. This suggests that also mechanisms

**Table 2 Selected outcomes of cardiopulmonary exercise testing in the post-EPaNIC 5-year follow-up cohort and controls**

	EPaNIC 5-year follow-up	Controls	<i>p</i> value
<b>CPET—peak exercise</b>	<i>N</i> = 361	<i>N</i> = 49	
VO <sub>2</sub> peak (ml/min/kg)	24.0 ± 9.7	31.7 ± 8.4	<0.001
VO <sub>2</sub> peak (%pred)	94 ± 31	123 ± 25	<0.001
Work rate (Watt)	126 ± 53	180 ± 56	<0.001
Work rate (%pred)	81 ± 26	112 ± 29	<0.001
Heart rate (beats/min)	128 ± 29	150 ± 21	<0.001
Heart rate (%pred HRmax)	80 ± 15	95 ± 12	<0.001
Heart rate reserve	31 ± 24	7 ± 20	<0.001
O <sub>2</sub> -pulse (ml/beat)	14.8 ± 4.8 <sup>a</sup>	17.1 ± 4.6	0.001
O <sub>2</sub> -pulse (%pred)	110 ± 31 <sup>a</sup>	118 ± 23	0.068
SpO <sub>2</sub> (%)	95 ± 2 <sup>b</sup>	96 ± 2	0.574
VEpeak (L/min)	67.3 ± 27.2	85.2 ± 23.4	<0.001
Ventilatory reserve (VEpeak/ MVV)	64 ± 18 <sup>c</sup>	66 ± 15	0.370
RER	1.17 ± 0.11	1.21 ± 0.09	0.025
ΔVO <sub>2</sub> /ΔWR (ml/W/min)	13.4 ± 5.1 <sup>d</sup>	13.6 ± 2.5 <sup>e</sup>	0.955
<b>CPET—anaerobic threshold</b>	<i>N</i> = 331	<i>N</i> = 49	
VO <sub>2</sub> AT (ml/min/kg)	15.3 ± 8.7	18.5 ± 6	0.015
VO <sub>2</sub> AT (%pred of VO <sub>2</sub> peak)	55 ± 16	71 ± 21	<0.001
VE/VCO <sub>2</sub> AT	31 ± 17.3	27.6 ± 3.4	<0.001

Continuous variables are depicted as mean (± standard deviation), categorical variables are depicted as number (percentages). Measurement available in <sup>a</sup>*N* = 357, <sup>b</sup>*N* = 338, <sup>c</sup>*N* = 355, <sup>d</sup>*N* = 345, <sup>e</sup>*N* = 21

CPET cardiopulmonary exercise testing, HR heart rate, VE ventilation, VO<sub>2</sub> oxygen consumption rate, AT anaerobic threshold, VCO<sub>2</sub> carbon dioxide production rate, RER respiratory exchange ratio, O<sub>2</sub>-pulse oxygen pulse, VE/VCO<sub>2</sub>AT ratio of ventilation to CO<sub>2</sub>-production at the anaerobic threshold, ΔVO<sub>2</sub>/ΔWR: metabolic efficiency, calculated as (VO<sub>2</sub>peak - VO<sub>2</sub>baseline)/peak work rate, MVV maximum voluntary ventilation

related to organ failure other than muscle strength contribute to impairment of the integrated exercise response. The number of patients with pulmonary factors contributing to exercise limitation was limited. These findings are in agreement with previous data [13, 14] suggesting that pulmonary function is not the main exercise limiting factor in ICU-survivors, notwithstanding some persistent abnormalities in static pulmonary function.

The observation that a significant amount of ICU survivors has reduced aerobic exercise capacity, not recovering between the 1- and 5-year follow-up period, may have important implications for the management of ICU survivors. Efforts to improve outcomes of ICU survivors after hospital discharge have been largely disappointing [46–48]. Multiple factors may explain the lack of success, notably population heterogeneity, possibly implicating differential rehabilitation potential and need for an individualized approach [49]. As aerobic exercise testing

can efficiently guide rehabilitation in various populations [22–25, 50], CPET may stratify patients, and individualise rehabilitation programs in survivors of critical illness, in particular those who experienced more severe organ dysfunction [51]. Presently, data from a single pilot study suggested benefit of tailored rehabilitation schemes on physical function and quality-of-life in ICU survivors, lost upon cessation of the program [52]. Evaluation in larger cohorts seems warranted to identify the window of opportunity for initiation, and feasibility of home-based continuation of such programs.

This study has several strengths. To the best of our knowledge, this is the largest study assessing aerobic exercise capacity in ICU survivors, and the first to repeatedly evaluate cardiorespiratory fitness up to 5 years following ICU stay. As the data were collected in a cohort that was included in a randomized trial, the ICU stay was well documented, allowing to assess and confirm the independent association of exercise limitation with in-ICU severity of organ failure. There are also some limitations. First, patients who performed CPET represented a subgroup of ICU survivors with less severe illness, shorter stays and better overall outcomes as compared to those who did not perform CPET. This was inevitable as patients unable to attend the follow-up clinic or with unstable medical conditions could not participate. Despite this bias, exercise limitation was highly prevalent, suggesting the true burden in the overall population of ICU survivors may be even higher. Second, by excluding submaximal CPETs from classification, we may have missed some patients unable to perform this degree of exercise due to muscular limitation. We lack invasive measurements and used a pragmatic protocol to categorise exercise-limiting factors ensuring feasibility in this large-scale research setting. We were able to identify major cardiopulmonary limitations but may have missed subtle limitations. Third, for the mixed model, as evidence on CPET in ICU-survivors is limited, unmeasured confounding cannot be excluded. In addition, selection bias may have occurred due to the recruitment strategy at intermediate time points which focused on long-stayers. However, mixed models can handle unbalanced designs and major bias seems unlikely as values at intermediate time points were not significantly lower than at 5 years. Fourth, as muscle strength was not systematically assessed during ICU-stay, we could not assess whether the impact of SOFA-max on exercise capacity was mediated by ICUAW. Fifth, as this was a secondary analysis, sample size was not modifiable. Sixth, our controls appeared relatively fit. However, we chose the reference equations described by Jones et al. [30], representing a “sedentary healthy state” [9,

**Table 3 Demographics, physical outcomes in the post-EPaNIC 5-year follow-up cohort and controls**

	EPaNIC 5-year follow-up					Controls			
	No CPET	N <sup>b</sup>	CPET	N <sup>b</sup>	p value		N <sup>b</sup>	p value <sup>a</sup>	
Test location, hospital	94 (30)	313	361 (100)	361	<0.001		49 (100)	49	NA
<b>Pulmonary function</b>									
FVC (%pred)	85 ± 24	306	103 ± 19	361	<0.001		114 ± 14	49	<0.001
FEV1 (%pred)	78 ± 24	306	94 ± 20	361	<0.001		108 ± 12	49	<0.001
Tiff	74 ± 10	306	74 ± 9	361	0.932		77 ± 6	49	0.022
TLC (%pred)	92 ± 15	82	98 ± 15	331	0.001		NA	0	NA
DLCO (%pred)	72 ± 19	97	81 ± 17	349	<0.001		NA	0	NA
<b>Muscle strength</b>									
MRC-sum score	60 (57–60)	307	60 (58–60)	361	0.001		60 (60–60)	49	<0.001
HGS (%pred)	77 ± 29	312	93 ± 21	359	<0.001		104 ± 19	49	<0.001
<b>Handgrip strength</b>									
Shoulder	86 ± 28	304	94 ± 22	355	<0.001		104 ± 27	49	0.002
Elbow	79 ± 23	305	89 ± 20	360	<0.001		103 ± 21	49	<0.001
Wrist	95 ± 27	298	102 ± 23	360	<0.001		109 ± 22	49	0.038
Hip	139 ± 40	297	148 ± 33	352	0.002		163 ± 36	49	0.004
Knee	53 ± 18	293	53 ± 15	340	0.794		65 ± 15	48	<0.001
Ankle	72 ± 21	299	73 ± 21	358	0.480		91 ± 22	49	<0.001
Knee extension (%pred) <sup>c</sup>	79 ± 28	79	86 ± 26	333	0.037		99 ± 30	46	0.002
MIP (%pred)	83 ± 32	299	95 ± 30	357	<0.001		105 ± 27	49	0.029
<b>Physical function</b>									
6MWD (%pred)	81 ± 22	206	95 ± 19	361	<0.001		115 ± 18	49	<0.001
<b>Quality of life</b>									
PCS	42 (32–52)	290	49 (39–55)	344	<0.001		56 (52–58)	49	<0.001
PF-SF36	60 (30–85)	306	80 (60–95)	357	<0.001		95 (90–100)	49	<0.001
MCS	55 (45–59)	290	55 (49–59)	344	0.689		58 (53–60)	49	0.025

Continuous variables are depicted as mean ± standard deviation or median (interquartile range) as appropriate, categorical variables are depicted as number (percentages)

FVC forced vital capacity, FEV1 forced expiratory volume in 1 s, TLC total lung capacity, VC vital capacity, DLCO diffusion capacity, MRC Medical Research Council sum score, HGS hand-grip-strength, HHD handheld dynamometry, MIP maximal inspiratory pressure, 6MWD six-minute-walk-distance, PF-SF36 physical function sub-score of the 36-item Short-Form Health score, MCS Mental Component Score, PCS physical component score

<sup>a</sup> p value for comparison of patients EPaNIC patients at 5-year follow-up who performed CPET and controls

<sup>b</sup> Number of patients for whom data are available

<sup>c</sup> Knee extension was assessed with Biodex

12], and therefore, a good benchmark for our patients, as we wanted to avoid overestimating the prevalence of abnormal exercise capacity. These reference values may be inappropriately low for more active healthy people [9, 53]. However, this issue, nor the size of the control population affects the overall conclusions as defining abnormal exercise capacity in patients was based on comparison with a widely accepted reference population [30] and not as a comparison to our controls. In addition, controls were not included in the mixed model evaluating the association between SOFA-max and VO<sub>2</sub>peak. Seventh, we did not study post-ICU events, which could potentially contribute to exercise

capacity. Finally, as our population was derived from an RCT, generalisability may be limited.

In summary, ICU survivors have impaired aerobic exercise capacity. Severity of organ failure independently associates with exercise performance throughout follow-up. Reduced muscle strength at follow-up also independently associates with reduced exercise capacity but did not explain the effect of severity of organ failure on this outcome. Although causal pathways explaining the lasting reduction in exercise capacity require further exploration, our data suggest a role for CPET in guiding rehabilitation programs in ICU survivors.



## Supplementary Information

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## Author contributions

Study concept and design: GH, NVA, KG, RG. Acquisition of data: GH, PM, YD, AW, MPC, JG, JW, PJW. Analysis and interpretation of data: NVA, GvDb, GH, KG, RG. Drafting of the manuscript: NVA, GH. Critical revision of the manuscript for important intellectual content: NVA, PM, YD, AW, MPC, JG, JW, KG, RG, PJW, GvDb, GH. Statistical analysis: GH, NVA. Obtained funding: GH, NVA, GvDb, MPC, JG. Administrative, technical support: PJW. Study supervision: GH, PJW, GvDb.

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## Declarations

### Conflicts of interest

The authors have no conflict of interest with the sponsors of the study.

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