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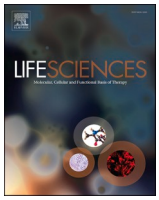

Manual dexterity, tactile perception and inflammatory profile in HCWs affected by long Covid: A case – control study

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1. Introduction

COVID 19 infection in many cases has left a disabling condition usually referred to as “Long Covid” or “Post-Acute Covid Syndrome (PACS)”. Even if a scientific unanimous consensus is still lacking, the WHO defines Long Covid as “the presence of symptoms 3 months after the initial SARS-CoV-2 infection, lasting for at least 2 months with no other explanation” [1].

The global prevalence of long Covid varies widely, from 5 % to 43 %, depending on the case definition, length of follow-up, self-reported symptoms or confirmed diagnoses [2,3], while risk factors include: older age, female sex, pre-existing medical conditions, obesity, and severity of acute illness [4–7].

Among the wide range of multiple ongoing health problems and manifestations which have been recognized as related to the syndrome, the neuropsychological ones ranked high and are grouped together under the term “Neuro Long Covid”. This category includes central and peripheral nervous system dysfunctions, psychiatric manifestations and executive deficits [8], that are not always easy to define instrumentally.

Healthcare workers (HCWs) constitute a high-risk population that presents a 24-fold higher probability of contracting COVID−19 than the general population [9], and may subsequently develop Long Covid syndrome depending on the above mentioned personal risk factors.

A number of studies have been carried out on these professionals still complaining symptoms at different time points after acute COVID 19 [7,10–16], many of them detailing the types of disorders and the specific occupation, and some also investigating the HCWs perceived work ability after recovery [12,13] but no study up to date, to the best of our knowledge, has objectively evaluated what might be the impact of long-term COVID condition on fine manipulation skills in HCWs, which is extremely important in this type of job.

Examples of activities and procedures that require a precise gesture include arterial or venous sampling, performing complex medications, detecting vital parameters and even participating in invasive manoeuvres on patients. For this reason, the topic of fine motricity in HCWs has been already investigated in the past, particularly in relation to the size and type of protective gloves, which, if inappropriate, can have a detrimental effect on fine motor skills [17,18], but has not been fully acknowledged yet in Long Covid condition.

The aim of the present study was to assess both fine manipulative skills and sensorineural perception in HCWs affected by Long Covid, coupled with systemic inflammation assessment, in order to evaluate whether secondary prevention measures are needed to restore sensorimotor abilities.

2. Material and methods

2.1. Study design and ethical aspects

This observational, controlled, quantitative and descriptive cross-sectional study was approved by the FVG's Unite Research Ethics Committee (approval number 245_2023H, ID 17328). All participants signed an informed consent before being included in the study; the study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Participants enrolment

At the beginning of November 2022, all ASUGI employees (n. = 6655) have been informed on the type and aim of the study via company e-mail. Each worker who showed interest in participating in the project and met the inclusion criteria was then enrolled. Inclusion criteria for

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Long Covid HCWs group (G1) were: previous COVID-19 confirmed via RT-PCR on nasopharyngeal swab (NPS) and persistence or new onset of symptoms (1 or more from those listed by (ISS) beyond 12 weeks after NPS negativization and still present at the beginning of the study, exclusion criteria: previous COVID-19 and symptoms still present but lasting <12 weeks. Inclusion criteria for HCWs never infected by Sars-CoV-2 group (G2): have been regularly tested for Sars-Cov2 by NPS according to the hospital safety protocol for the pandemic period and resulted always negative.

2.3. Data collection

Each participant underwent a questionnaire and a series of instrumental evaluations described in detail below, in order to assess: general health status; upper limbs sensorimotor functions, body composition, systemic inflammation. The G1 underwent also a Long Covid - symptoms questionnaire.

1. **General health status and Long Covid symptoms questionnaires**: data on age, sex, weight and height, smoking habits, Sars-Cov-2 vaccination status, comorbidities, pharmacotherapy and job descriptors were collected. The G1 group was also asked to fill in a questionnaire on ongoing symptoms, according to those described by Istituto Superiore di sanità [19]. (supplemental material 1 and 2)
2. **Bioimpedenziometric body composition (BIA-ACC®** device, Biotekna srl, Venice, Italy): Body composition was measured using a bioelectrical impedance analysis (BIA-ACC® device - Biotekna srl. Venice, Italy) which is simple, quick, non-invasive, and reliable [20]. After a 10 min period of acclimatization the subject was tested in supine position. One electrode was attached on the right hand (between the dorsal surface of the metacarpal heads and wrist) and one more electrode on the right foot (between the dorsal surface of the metatarsal heads and ankle) to measure by passing a dual frequencies safe signal through the body ("low frequency" of 1.5 kHz and a "high frequency" of 50 kHz), which ensure an accurate estimate of the extracellular compartment. Parameters assessed using this device included: Body mass index (BMI, kg/cm^2), total body water (TBW) extracellular and intracellular water (ECW and ICW), fat mass (FM) and lean body mass (FFM): measured both in kilograms (Kg) and as a percentage of body weight (BW%), specific adipose measurements, including Abdominal Adipose Tissue (AAT, cm^2) and Intramuscular Adipose Tissue (IMAT), Bone Mass (BM) and Skeletal Muscle mass (SM): both in kg and percentage of fat to lean mass (FFM%), S-Score: a measure of the standard deviation of skeletal muscle mass compared to healthy reference subjects aged 25 to 30 years, T-Score: a measure of the standard deviation of mean bone mass compared to healthy young reference subjects. Contraindication to undergo the exam: all pacemaker wearers and/or people with epilepsy. The values were obtained from the device which is programmed to run on the manufacturer's prediction equation.
3. Sensorimotor functions quantitative assessment:

- **Hand grip force through Jamar dynamometer:** The maximum grip force of the dominant hand was measured using an hydraulic dynamometer (model 5030 J1). The subject was asked to maintain a seated position, with the elbows flexed at 90°, the wrist in neutral position and the forearm supported by a support surface, and to squeeze the dynamometer as hard as possible three times, with an interval of 10 s between each squeeze. The average value of the three attempts was recorded and expressed in Newtons.
- **Finger pincer grip strength through Pinch dynamometer**: the maximum grip strength ('in pinch') between the first and second fingers of the dominant hand was evaluated. During the test, the subject maintains a sitting position, with the elbows flexed at 90°, the arm slightly extended and the forearm in neutral position. There were performed the two-finger or two-point pinch test (important for picking up an object, such as a coin from the ground). In this test, the pinchmeter is placed between the tip of the thumb and the tip of the index finger and the subject is asked to squeeze the instrument with as much force as possible. Again, as with the hand grip force, for each test the grip was performed three times, with a 10-s interval between one attempt and the next [21].
- **Cutaneous esthesiometric thresholds through Semmes-Weinstein** monofilaments (SWMFT): fibers diameters between 0.127 and 1.143 mm, corresponding to a force of 0.068–447 g (Touch TestTM Sensory Evaluator Stoelting, measuring 2.83–6.65, Co, IL, USA) were used. The fingertips of the 1st and 2nd fingers were tested, bilaterally, to assess the function of the median nerve, while 5th finger and hypothenar eminence for the ulnar nerve and the dorsum for the radial nerve. While the patient turned their gaze away from their hand, the monofilament was placed perpendicular to the skin surface of the fingertips and lightly pressed (so that the filament was bent or arched) for approximately 1.5 s with constant pressure. This procedure was applied three times on the same skin site to evoke the stimulus. The test is started with the thinnest monofilament, after which, if the stimulus is not felt by the subject, the test is continued with the next largest monofilament.
- **Manual dexterity though Purdue Pegboard Test (PPT):** the researcher gave the subject standardized verbal instructions on how to carry out the test, as well as a brief demonstration. Then, before the start of the assessment, the subject tried to use the perforated panel. To carry out the test, the subject, starting with the dominant hand, picked up the pins placed in a bowl on the corresponding side of the panel and tried to place as many of them as possible in the prepared holes within 30 s. The test was then also performed with the other hand and with both hands simultaneously. The score was calculated according to the number of pegs inserted with the dominant hand, with the non-dominant hand and with both hands. These scores were also added together. Next, the assembly test was performed, which consisted of a standardized sequence of assembling the pegs, washers, and collars, using both hands, in one minute of time. The score for this last test was determined by the total number of pegs, washers and collars correctly fitted.

4. **Blood analysis:** each participant underwent complete blood count, coagulation and systemic inflammation indices (fibrinogen, d-dimer, CRP, ferritin) a cytokine panel (IL- 1, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, INF-γ, VEGF, MCP-1, EGF) and antibody title against SARS-CoV-2 (Diasorin Liaison® Sars-Cov-2 Trimeric - S - Igg). For the cytokine assay, 10 ml of blood was collected intravenously in Vacutainer tubes fortified with ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. The samples were subsequently centrifugated to separate plasma, that was used to run flow cytometry (Randox Laboratories Ltd. array kit - Tri level control). All procedures were performed according to the guidelines provided by the manufacturer. Exclusion criteria for blood samples: oncological, immuno-reumatological and allergological subjects were excluded as results may be influenced by underlying diseases.

3. Statistical analysis

Continuous data were reported as means (SD) or as medians (IQR) and compared using *t*-test or Wilcoxon rank sum test if normally or not normally distributed, respectively. Categorical and binary data were compared using Pearson's chi-square test or Fisher's exact test as normally or not normally distributed. All analyses were performed using Stata® software V. 16 (StataCorp LP, College Station, TX, USA). All *p*-values were two-sided, and values <0.05 were deemed statistically significant.

Table 1
Participants demographic and clinical characteristics. Continuous results are reported as mean (SD) or median (25–75 IQ range) and compared using *t*-test or Wilcoxon Rank sum test if normally or not normally distributed. Respectively. Dichotomous variables are reported as number (%) and compared using Chi-square test. In bold significant results ($p < 0.05$).

	PACS (n. obs = 58)	CONTROLS (n. obs = 53)	p
Age (yrs)	51.5 (42–57)	50 (37–58)	0.65
Female sex	45 (77.6 %)	43 (81.1 %)	0.82
BMI	25.7 (22–27.5)	24.8 (21.3–27.5)	0.32
Sars-cov-2 vaccinated	56 (9.6 %)	52 (98.1 %)	0.36
Sars-cov-2 antibody titer	17,916.35 (9127.5–36,621.4)	6569.6 (1694–19,452.2)	**0.002**
Vaccine doses administered	2.9 (0.63)	3.25 (0.48)	**0.001**
Time from COVID-19 to evaluation (days)	487 (286) 419.5 (269–730)		

4. Results

A total of 6655 HCWs workers have been reached and informed as regard the aim and content of the study. Of them 111 were included after selection by inclusion/exclusion criteria, $n = 58$ as Long Covid group (G1) and $n = 53$ as healthy controls (G2).

Table 1 shows demographic and clinical characteristic data, while fig. 1 shows Long Covid most complained symptoms. Cases have been evaluated at a mean time of 16 (SD 9.4) months after the acute infection, of them $n = 23$ (40 %) had ongoing symptoms from >18 months, 9 (16 %) between 12 and 18 months, 16 (28 %) between 6 and 12 months and only 10 (17 %) between 12+weeks and 6 months.

Antibody titer was significantly higher in Long Covid group, while the vaccine doses were higher in control group, as expected.

4.1. Manual dexterity and force: Purdue Pegboard, Pinch and Jamar tests

Table 2 and Fig. 2 show fine manipulation skills and hand and first two fingers grip strength. Long Covid subjects were significantly less able to perform the right-handed pin insertion task (almost all were right-handed), the hands together task and the assembly task compared

Table 2
Manual dexterity assessment through Purdue Pegboard Test (PPT) and hand and finger force assessment through Pinch and Jamar dynamometers.PACS=Post Acute Covid Syndrome. Data are reported as median (IQR) scores (PPT) or Kg (Pinch – Jamar) and compared using Wilcoxon rank sign test (not normally). In bold significant results.

	PACS (n = 58)	CONTROLS (n = 53)	p
Right hand	13 (12–15)	14 (13–15)	**0.04**
Left hand	12 (11–14)	13 (12–14)	0.15
Both hands	10 (9–11)	11 (10−12)	**0.03**
Right+Left+Both	36 (32–40)	38 (35–42)	0.08
Assembly	24 (20−30)	28 (23−33)	**0.03**
Pinch	4 (3–5,5)	5 (4,5–5)	**0.03**
Jamar	28 (22–34)	30 (24–34)	0.32

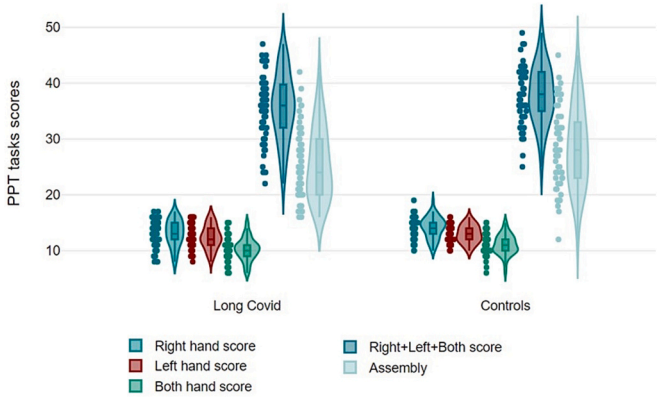

Fig. 2. Violinplot of Purdue Pegboard Test (PPT) scores among cases and controls. Long Covid vs Controls.

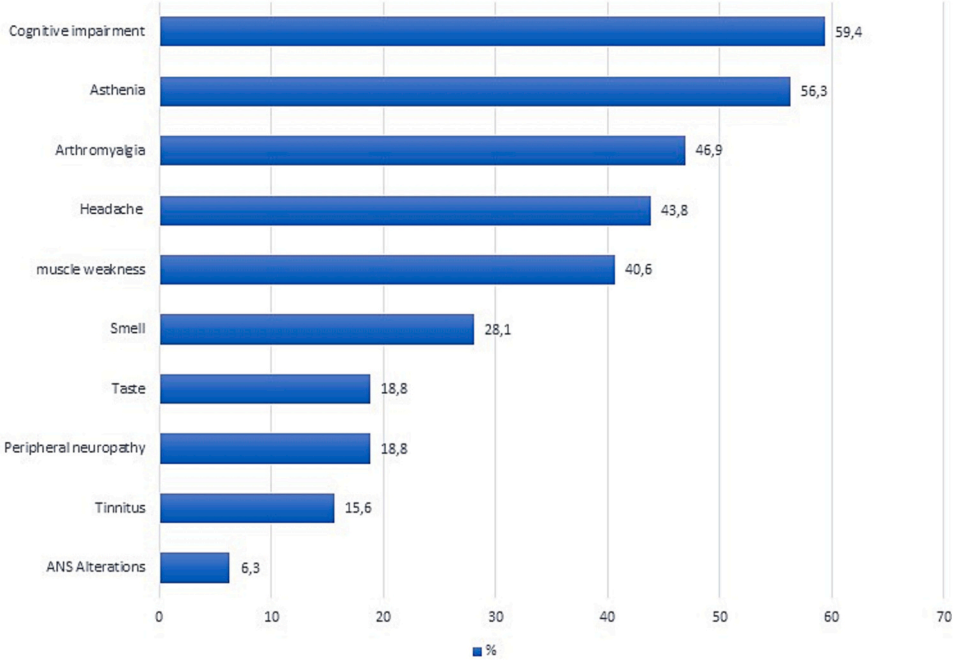

Fig. 1. Long Covid systemic and neurological symptoms, reported as % and assessed as defined by Istituto Superiore di Sanità [19]

Table 3
Esthesiometric thresholds assessed through Semmes-Weinstein Monofilament Test (SWMT). For each finger smallest perceivable grade (SPG) has been assessed for PACS and Controls. PACS = Post Acute Covid Syndrome. The SWMT 1.65, 2.36, 2.44, 2.83, 3.22 and 3.61 correspond to a target force of 8, 20, 40, 70, 160 and 400 mg, respectively. Normal perception range: 8-70 mg. Data has been compared with Fisher exact test. In bold significant results.

	1.65 filaments		p	2.36 filaments		p	2.44 filaments		p	2.83 filaments		p	3.22 filaments		p	3.61 filaments		p
	PACS (58)	CONTROLS (53)		PACS (58)	CONTROLS (53)		PACS (58)	CONTROLS (53)		PACS (58)	CONTROLS (53)		PACS (58)	CONTROLS (53)		PACS (58)	CONTROLS (53)	
I Finger right	1 (1.7 %)	4 (7.5 %)	0.14	9 (15.5 %)	20 (37.7 %)	**<0.01**	20 (34.5 %)	16 (30.2 %)	0.63	20 (34.5 %)	8 (15.1 %)	**0.02**	4 (6.9 %)	5 (9.4 %)	0.62	3 (5.2 %)	0 (0.0 %)	0.09
I Finger left	2 (3.4 %)	6 (11.3 %)	0.11	18 (31.0 %)	20 (37.7 %)	0.46	18 (31.0 %)	20 (37.7 %)	0.46	15 (25.9 %)	6 (11.3 %)	0.05	3 (5.2 %)	1 (1.9 %)	0.35	1 (1.7 %)	0 (0.0 %)	0.34
II Finger right	1 (1.7 %)	5 (9.4 %)	0.07	16 (27.6 %)	16 (30.2 %)	0.76	27 (46.6 %)	21 (39.6 %)	0.46	7 (12.1 %)	9 (17.0 %)	0.46	5 (8.6 %)	2 (3.8 %)	0.29	0 (0.0 %)	0 (0.0 %)	
II Finger left	1 (1.7 %)	4 (7.5 %)	0.14	26 (44.8 %)	26 (49.1 %)	0.66	16 (27.6 %)	18 (34.0 %)	0.47	9 (15.5 %)	4 (7.5 %)	0.19	4 (6.9 %)	1 (1.9 %)	0.20	0 (0.0 %)	0 (0.0 %)	
V Finger right	2 (3.4 %)	11 (20.8 %)	**<0.01**	25 (43.1 %)	19 (35.8 %)	0.44	19 (32.8 %)	16 (30.2 %)	0.77	9 (15.5 %)	5 (9.4 %)	0.33	2 (3.4 %)	2 (3.8 %)	0.93	0 (0.0 %)	0 (0.0 %)	
V Finger left	8 (13.8 %)	12 (22.6 %)	0.23	31 (53.4 %)	25 (47.2 %)	0.51	14 (24.1 %)	12 (22.6 %)	0.85	1 (1.7 %)	2 (3.8 %)	0.51	2 (3.4 %)	2 (3.8 %)	0.93	0 (0.0 %)	0 (0.0 %)	
Dorsum right	41 (70.7 %)	44 (83.0 %)	0.13	9 (15.5 %)	6 (11.3 %)	0.52	2 (3.4 %)	1 (1.9 %)	0.61	2 (3.4 %)	2 (3.8 %)	0.93	2 (3.4 %)	0 (0.0 %)	0.17	1 (1.7 %)	0 (0.0 %)	0.34
Dorsum left	38 (65.5 %)	45 (84.9 %)	**0.02**	9 (15.5 %)	6 (11.3 %)	0.52	4 (6.9 %)	2 (3.8 %)	0.47	2 (3.4 %)	0 (0.0 %)	0.17	2 (3.4 %)	0 (0.0 %)	0.17	2 (3.4 %)	0 (0.0 %)	0.17
Hypotenar right	5 (8.6 %)	6 (11.3 %)	0.63	28 (48.3 %)	27 (50.9 %)	0.78	15 (25.9 %)	16 (30.2 %)	0.61	5 (8.6 %)	4 (7.5 %)	0.84	3 (5.2 %)	0 (0.0 %)	0.09	1 (1.7 %)	0 (0.0 %)	0.34
Hypotenar left	3 (5.2 %)	6 (11.3 %)	0.24	32 (55.2 %)	31 (58.5 %)	0.72	13 (22.4 %)	12 (22.6 %)	0.98	5 (8.6 %)	4 (7.5 %)	0.84	3 (5.2 %)	0 (0.0 %)	0.09	1 (1.7 %)	0 (0.0 %)	0.34

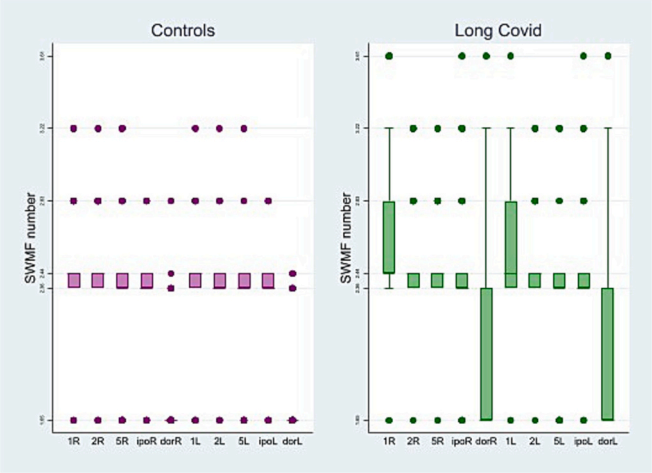

Fig. 3. Boxplot of the smallest esthesiometric perceivable grade (SPG) assessed through Semmes-Weinstein Monofilament Test (SWMT) in cases and controls in different areas of the hand. 1R= 1st right finger and 2R= 2nd right finger (right median nerve), 5R= 5th right finger and ipoR= right ipotenar eminence (right ulnar nerve), dorR= right dorsum of the hand (right radial nerve); 1L= 1st left finger and 2L= 2nd left finger (left median nerve), 5L= 5th left finger and ipoL= left ipotenar eminence (left ulnar nerve), dorL= left dorsum of the hand (left ulnar nerve).

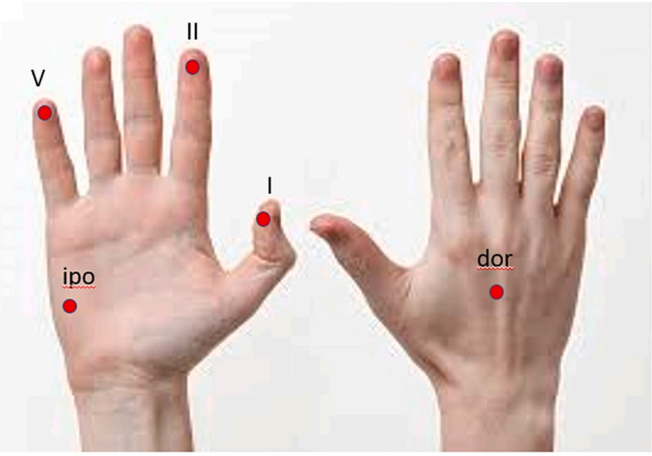

Fig. 4. Specific areas tested through Semmes-Weinstein Monofilament Test (SWMT).

to controls, moreover they also showed low strength in the finger grip test.

4.2. Sensorineural perception: Semmes Weinstein monofilaments

Table 3 and Fig. 3 show a comparison of the smallest perceivable grade (SPG) of esthesiometric perception for each point tested (refer to Fig. 4) for Long Covid and Control groups. First and second finger reflect the median nerve fibers sensitivity, fifth finger and hypothenar eminence reflect the ulnar nerve fibers sensitivity, while the dorsum of the hand reflects the radial nerve fibers sensitivity. Comprehensively the sensory thresholds are in the normal range values, with spot areas of higher thresholds in Long Covid group, as regard all three nerves tested (Table 3).

4.3. Body composition: BIA-Acc bioimpedance assessment

Table 4 shows the body composition analysis. No significant differences between the two groups have been observed.

Table 4
BIA analysis. Body composition values among the two groups. Data are reported as Median (IQR) and compared using Wilcoxon rank sum test since not normally distributed. PACS = Post Acute Covid Syndrome. BMI = body mass index. TBW % = % of Total Body Water. ECW% = % Extracellular Body Water. ICW% = % Intracellular Body Water. FM% = % Fat Mass. ECMatrix % = % Extra Cellular Matrix. HPA Index: Hypothalamus-Pituitary gland axis. T score: reflects bone density. S score: reflects muscle density. IMAT = Intra-Muscolar-Fat-Tissue. AT. % = Adipose Tissue. AAT.% = Abdominal Adipose Tissue. Fitness Index: reflects level of subject's training.

	Reference values	PACS (n = 58)	CONTROLS (n = 53)	p
BMI (kg/m^2)	18.5 to 24.9	25.7 (22–27.5)	24.8 (21.3–27.5)	0.32
TBW%	50–65 % BW	41 (38–46)	43 (39–45)	0.36
ECW%	40 % TBW	48.5 (44–51)	49 (46–52)	0.43
ICW%	60 % TBW	51.5 (49–56)	51 (48–54)	0.43
FM%	min 7 % - max 25 %	35 (30–39)	33 (26–38)	0.20
ECMatrix %	15–20 % BW	24 (20–28)	24 (21–29)	0.33
HPA index	> 3.5	1.9 (1.4–2.3)	2.1 (1.5–2.5)	0.25
< 2.5		46 (79.3 %)	38 (1.72 %)	0.66
2.5–3.5		10 (17.2 %)	13 (24.5 %)	
> 3.5		2 (3.4 %)	2 (3.8 %)	
T score	Normal <−1. osteopenia −1 -2.5. osteoporosis ≤2.5	-1 (−1.5 - -4)	−1.2 (−1.6 –0.3)	0.53
S score		−1 (−1.5 –0.1)	−1.2 (− 1.7–0.1)	0.59
IMAT	max 2 % BW. ideal <1.5 % BW	2.2 (1.9–2.5)	2.1 (1.7–2.4)	0.17
AT.%	max 31 % BW	44.2 (36.9–48.4)	41.8 (33.1–47.4)	0.18
AAT (cm^2)		398.4 (286–546.8)	359 (222.2–456.4)	0.17
Fitness index	min 0.54. ideal 1.20	0.58 (0.47–0.77)	0.65 (0.51–0.77)	0.22

4.4. Systemic low grade inflammation and cytokines panel

Table 5 show the comparison of blood counts, inflammatory markers and cytokines levels between two groups. Eosinophils (absolute numbers and %) are significantly higher in Long Covid group, while IL6 is near significantly higher levels ($p = 0.05$).

5. Discussion

This study involved a sample of $n = 58$ Long Covid HCWs examined approximately 16 months after COVID-19 and $n = 53$ healthy controls, comparable in terms of age, sex and BMI. Among cases cognitive impairment, asthenia and muscle weakness rankest highest in the symptoms still complained at the time of assessment.

We used the Purdue Pegboard Test to quantify fine manipulative skills, finding a relevant decline in manual dexterity in workers affected by Long Covid compared to controls and also a reduction in grip strength of the first two fingers (Pinch test), while sensorineural perception was in normality range (Semmes Weissen Monofilament Test).

These findings are in line with the other few studies that assessed this topic in Long Covid patients, as will be discussed in greater detail below.

Manual dexterity is dependent upon the interaction of numerous brain regions, including the pre-motor and motor cortex, cerebellum, basal ganglia, corticospinal tracts, and peripheral nerves. The final outcome also depends on the interaction of visuospatial, sensory, and executive functions [22], coupled with musculoskeletal efficiency. Furthermore, bimanual coordination necessitates the involvement of additional cerebral regions, including the primary sensorimotor and prefrontal cortex [23,24] and the motor cingulate [24]. In long Covid

Table 5
Comparison of blood parameters and a cytokines panel between PACS group (Post Acute Covid Syndrome) and never infected group (Controls). Data are reported as Median (IQR) and compared with Wilcoxon rank sum test since not normally distributed. In bold significant results.

	PACS (n = 58)	CONTROLS (n = 53)	p
White blood cells (x 10^3/mcl)	6.38 (5.55–7.11)	6.16 (5.07–7.39)	0.95
Red blood cells (x 10^6/mcl)	4.56 (4.41–4.79)	4.73 (4.4–5.1)	0.38
Hemoglobin (g/dl)	13.6 (12.9–14.5)	14 (12.6–15)	0.73
Hematocrit (%)	41.6 (40.3–43.4)	43.3 (39.6–45.3)	0.31
MCV (fl)	90.8 (87.8–93.4)	91.8 (89.1–93.8)	0.43
MCH (pg)	29.7 (29.1–30.8)	30.5 (28.5–31.2)	0.31
Platelets (x 10^3/mcl)	261 (225–293)	255 (232–294)	0.79
Neutrophils (%)	55.7 (49.3–61.3)	55.9 (50.6–61.4)	0.76
Lymphocytes (%)	30.6 (27–37.1)	33.6 (27.1–37.9)	0.52
Eosinophils (%)	2.8 (1.8–4.1)	1.9 (1.1–2.8)	**<0.01**
Basophils (%)	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.78
Neutrophil count (x10^3/µL)	3.37 (3.0–4.0)	3.45 (2.75–4.4)	0.78
Lymphocyte count (x10^3/µL)	1.96 (1.7–2.2)	2.09 (1.63–2.48)	0.35
Eosinophils count(x10^3/µL)	0.17 (0.1–0.22)	0.11 (0.07–0.18)	**0.02**
Basophils count (x10^3/µL)	0.04 (0.04–0.06)	0.05 (0.03–0.06)	0.93
CRP (mg/L)	1.6 (0.8–3.1)	1.35 (0.6–2.5)	0.27
Ferritin (mcg/L)	37.4 (17.2–68.7)	46.8 (20.7–91.1)	0.39
Fibrinogen (mg/dL)	304.5 (255–356)	316 (273–351)	0.25
D-dimer (ng/mL)	318.5 (245–442.5)	281 (228–387)	0.06
Cytokines (pg/mL)			
IL2	0 (0–3.5)	0 (0–3.1)	0.44
IL4	1.45 (1.08–1.86)	1.58 (1.45–1.77)	0.14
IL6	1.79 (1.32–2.94)	1.27 (1.16–1.74)	**0.05**
IL8	11.0 (8.55–19.3)	11.68 (8.81–17.6)	0.85
IL10	0 (0–0)	0 (0–0)	0.83
VEGF	215.3 (144.6–336.5)	227.1 (112.6–303.2)	0.57
INF g	0 (0–0)	0 (0–0)	0.65
INF a	2.49 (2.06–3.4)	2.7 (2.4–3.5)	0.61
IL 1 a	0.52 (0–0.68)	0 (0–0.55)	0.28
IL 1 b	0 (0–1.63)	0 (0–0)	0.12
EGF	73.4 (40.4–98.5)	70.8 (32.6–94.0)	0.86
MCP1	305.3 (247.8–389.3)	375.8 (311.1–407.7)	0.17

subjects many of these areas show hypomethabolism, as demonstrated in brain fRMN studies ([25–26] Hugon, Guedi), but no many investigations have yet quantified the clinical impact of such findings on patient's executive skills. Interestingly, Chang L. et al. [27], found decreased manipulative skill in an exploratory study involving $n = 29$ Long Covid, which moreover showed a compensatory activation of nondominant brain regions during specific tasks at brain fMRI (Blood Oxygenation Level Dependent-fMRI) compared to controls (9-Hole Pegboard Test, dominant hand: d = −0.79, 95 % CI -0.19 to −0.38, $p = 0.007$).

Moreover, Hayward and colleagues [28], found that long Covid subjects ($n = 53$) complaining neuropsychiatric disorders and evaluated approximately 8 months after COVID-19 (mean ± SD, 242 ± 156 days) had decreased typing speed coupled with a deficit in procedural memory, while early learning was comparable to controls ($n = 87$ pandemic and $n = 105$ pre-pandemic sex and age-matched subjects).

Finally, a case-case-control study evaluated manual dexterity and bimanual coordination in $n = 21$ Long Covid subjects 16 months after acute infection (mean ± SD, 16 ± 6 months) and compared results with those of $n = 17$ 16-years duration ME/CSF patients (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) and $n = 19$ healthy controls. Results showed that both the patients group performed poorer and comparable Purdue Pegboard scores compared to controls [29], although the duration of the disease in people with the two types of illness varied greatly.

The evidence from the aforementioned studies collectively corroborates the hypothesis that individuals presenting with long-Covid symptoms exhibit a decline in the efficiency of basic executive functions. Furthermore, this impairment appears to be sustained, as documented in both studies at 8 and 16 months post-acute infection.

As regards the sensorineural upper limb assessment, we found that the esthesiometric thresholds tested using Semmes Weinstein Monofilaments in the areas innervated by the median, ulnar and radial nerves were within the normal range and comparable to controls, with only sporadically higher thresholds in the Long Covid group. These findings are in contrast with those of other studies that have identified peripheral neuropathies in individuals with Long Covid [30–33]. Additionally, the results differ from those of Tereshko Y et al. [34], who evaluated sensorineural function through SWMT in $n = 30$ HCWs three months after contracting the virus. Their findings indicated a subclinical decline in tactile perception, suggesting a potential impairment of A-beta nerve fibers even in individuals who had recovered from the infection.

In evaluating the presence of systemic low-grade inflammation, our findings revealed no notable abnormalities in the haematological parametersin Long Covid group, with the exception of a distinctly elevated eosinophil count and a marginal increase in IL-6 levels. This is in line with a recent review and meta-analysis [35], which confirms that increased levels of IL-6 are associated with Long Covid and may be one of the biomarkers to identify the Long Covid phenotype where general and neurological complaints are prevalent [36], as were our cases. With regard to eosinophilia, there are indeed no studies of Long Covid assessed at a time far from acute infection which showed similar findings, with the sole exception of a 3 and 6 months follow up study after acute infection on $n = 18$ patients, where eosinophils and neutrophils were found elevated in cases [37]. Systemic inflammation could also be supported by extracellular matrix [38,39] and adipose tissue, especially the abdominal one that has been demonstrate to generate more inflammatory interleukines [40,41]. At body composition assessment we found that Long Covid HCWs were on average overweight, whereas the controls were in normal range, but we did not find a statistically higher BMI in the cases, nor an excess of total or abdominal adipose tissue or extracellular matrix.

6. Conclusions

Neuro-Long Covid is an entity very difficult to assess and objectivate, since the symptoms are very variable and multifaceted, but could be very disabling for everyday life and working ability of affected people. This late time point assessment (16+ months) on long Covid healthcare workers found a substantial recovery in esthesiometric upper limbs perception and a close to resolution systemic inflammation but a still compromised manual dexterity. It is important to objectify this aspect since it is not detectable during a common patient's clinical examination, but it can significantly impact working life of people involved in fine manipulative jobs, such as HCWs and others. Rehabilitative programs followed by instrumental reassessment should be considered to help these patients completely recover from fine motor impairment, evaluating tailored strategies which could both stimulate central nervous system motor areas, reducing muscle weakness and enhance visuomotor coordination.

CRediT authorship contribution statement

Marcella Mauro: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Nicoletta Bestiaco:** Writing – original draft, Investigation, Data curation. **Elisa Zulian:** Investigation, Data curation. **Maria Margherita Markežič:** Data curation. **Ilaria Bignolin:** Data curation. **Francesca Larese Filon:** Formal analysis.

Ethics statement

This study has been approved by the Unite Research Ethics Committee of FVG (approval number 245_2023H, ID 17328).

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Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2024.123234.

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