Project description: call for proposals NRP 78 "Covid-19"

Submission deadline: 25 May, 2020, 17:00 CET

Applicants Name, first name	(10)(2e)
Other applicant(s) Name, first name	(10)(2e)
Project title (English)	INCOVO study: **I**mpact of **N**utritional status on **COV**ID-19 infection **O**utcomes

Please indicate which research modules are the most relevant to your project:

- ☐ **Module 1:** Basic aspects of SARS-CoV-2 biology, pathogenicity and immunogenicity
- ☐ **Module 2:** New approaches in COVID-19 epidemiology and disease prevention
- ☐ **Module 3:** COVID-19 vaccine, drug development and diagnostics
- ☒ **Module 4:** Clinical COVID-19 research and therapeutic interventions

1. Project summary (maximum 1 page)

There is some confusion regarding the risk factors for in-hospital morbidity and mortality among SARS-CoV-2 (COVID-19) infected patients. Malnutrition, a highly prevalent condition in patients admitted to the hospital and a recognized risk factor for in-hospital morbidity and mortality, has seldom been studied. Only two monocentric, small-sampled Chinese studies have suggested that malnutrition is a risk factor for deleterious outcomes among COVID-19 infected patients, independent from obesity. Whether this finding can be replicated in other settings has not been evaluated; also, the effect of nutritional management on in-hospital outcome has not been studied.

We aim to conduct a retrospective, international multicentre observational study to 1) identify the relationship between nutritional status at hospital admission and in-hospital outcome, and 2) study the impact of nutritional management during hospitalisation on in-hospital outcome [admission at the intensive care unit (ICU), length of ICU and hospital stay, and in-hospital mortality) of COVID-19 infected patients. We will rely on a large network of participating centres where cases of COVID-19 have been or are currently being admitted. All centres have collected information on nutritional status, which can be retrieved from electronic medical records (EMRs). To our knowledge, this will be the sole network specifically focusing on the association between malnutrition and in-hospital outcomes of COVID-19 patients. There are six Swiss, eight Portuguese, two Brazilian, one Canadian and one Iranian participating centres, with an expected number of cases >5,000 (statistical power >90%). Other centres in Peru, Iran, Australia and the USA have been invited. The responsible investigator has a 20-year experience in nutritional research and has received previous funding from the SNF regarding nutrition.

All patients ≥18 years with confirmed COVID-19 infection by validated methods and with a length of stay ≥24 hours will be eligible. Patients will be identified from querying EMRs at the different study centres. All data are part of the clinical routines of the participating centres. To comply with local regulations and to minimize risk, all data analyses will be performed on-site: statistical codes importing/checking the data and analysing it will be provided for each collaborating group, which will apply them. The resulting metadata will then be transmitted to the coordinating centre, where it will be re-checked and meta-analysed. The expected duration of the study is 18 months. Four objectives will be attained:

1. **Estimate the nutritional status of hospitalized COVID-19 infected patients.** Prevalence rates and 95% confidence intervals of malnourished patients will be assessed overall and by gender and age group.
2. Estimate the associations between nutritional status and admission to the ICU, the rate of intubation, the length of stay and in-hospital mortality. Within each centre, the associations between malnutrition status and the different outcomes will be assessed using bivariate and multivariable methods, adjusting for confounders such as age, gender, comorbidities (hypertension, diabetes mellitus...) and therapy.
3. Describe the nutritional management of hospitalized COVID-19 infected patients. Within each centre, the different types of nutritional management (i.e. fractionated meals, oral nutritional support, enteral or parenteral nutrition) will be described, overall and stratifying on gender, age group, and ICU stay.
4. Assess the impact of nutritional management on admission to the ICU, the rate of intubation, the length of stay and in-hospital mortality. Within each centre, the associations between nutritional management (yes/no) and the different outcomes will be assessed using bivariate and multivariable methods.

The goal of this study aligns perfectly with the aims of the National Research Program NRP 78, specifically to identify new risk factors for severe COVID-19 disease and to improve the clinical characterization, management, and outcomes of affected patients, in particular in the ICU. Results will be submitted to gold open-access journals; press reports will be sent to selected media partners and distributed to the collaborating centres for translation and dissemination in the local media. Other channels (centres' websites or Twitter) will also be used. We hope that the knowledge obtained by this study will be largely distributed in the clinical field and will implement the existing guidelines on COVID-19 nutritional management by providing long-awaited evidence-based data.

2. Project plan (maximum 10 or 15 pages, respectively)

2.1 State of research in the field

Over the last months of COVID-19 outbreak; and due to the urgent public health situation, many studies aimed to identify risk factors of severe forms of COVID-19 disease. The initial period saw many clinical conditions being considered as risk factors [1,2] or not [3]. Most of these findings were obtained in monocentric, small sampled studies, and were not confirmed in subsequent studies or meta-analyses [4-6]. Currently, there appears to be some agreement regarding the main clinical risk factors that lead to severe cases of COVID: age or 65, male sex [7], smoking [6], presence of comorbidities (i.e. diabetes mellitus, hypertension, previous coronary heart disease or chronic obstructive pulmonary disease) [5,7,8] and obesity [9-12]. The impact of obesity on COVID-19 disease severity could be due to several mechanisms: a higher baseline inflammatory status among obese subjects [13], which would make them more prone to develop a "cytokine storm" [14]; a lower respiratory capacity [15], which would lead to a more severe disease status; an increased lipid peroxidation [16] and a higher angiotensin-converting enzyme 2 (ACE2 - the functional receptor for COVID-19) in the adipose tissue [17,18], which would act as a reservoir for the virus, thus increasing shedding, immune activation and cytokine amplification [19].

Nutritional status as a risk factor for COVID-19 infection:

Malnutrition is the most important cause of immunodeficiency worldwide [20]. Already during the Crimeria war in 1859, Florence Nightingale reported English soldiers starving among plenty of food [21]. Indeed, at least four out of ten hospitalized patients present with some type of malnutrition [22,23], including obese subjects [24]. Malnutrition rates increase with age [24] and in presence of multimorbidity [25]. Malnutrition leads to increased hospital length of stay (LOS) [26,27], in-hospital mortality [27,28] and health costs [28,29]. Even in Switzerland, a country with a generous health system, malnutrition is a common [24] and a strong risk factor for in-hospital morbidity and mortality [28,30]. Importantly, malnutrition is frequently underestimated in hospital practice, leading to an underreporting of the condition [31,32]. We have previously shown that clinical data obtained directly from electronic medical records (EMR) is more valuable to estimate prevalence of malnutrition than obtained from hospital discharge data [33].

Malnutrition impacts several metabolic systems and has been suggested to be a virulence factor for the COVID-19 [34]. **Figure 1** summarizes the possible mechanisms by which malnutrition could impact the bodily response to COVID-19 infection [34]. Based on these elements, the European Society of Parental and Enteral nutrition released and expert statement and practical guidance to help health professional for both identification of at risk and malnourished patients with COVID-19 infection and to guide nutritional management of this population [35].

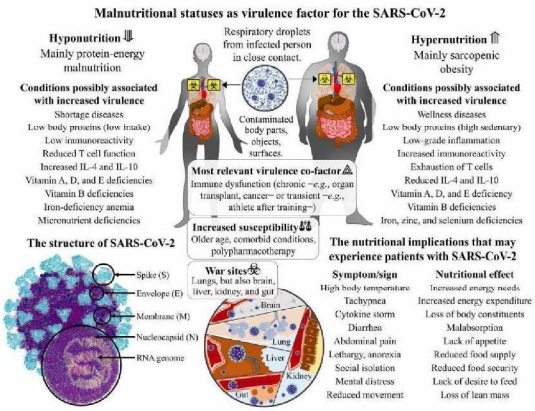

Figure 1: *possible mechanisms of malnutrition as risk factor for COVID-19. Taken from [34].*

Patients at risk of malnutrition can be detected using a variety of tools, and over 20 of them have been reported [36-38]. The most commonly used are the Malnutrition Universal Screening Tool (MUST), the Mini Nutritional Assessment (MNA) and the

Nutritional Risk Screening (NRS or NRS-2002) [39], the characteristics of which are indicated in **table 1**.

MUST	Rating of three clinical parameters: • BMI (kg/m²): >20=0; 18.5-20=1; <18.5=2 • Weight loss: <5%=0; 5-10%=1; >10%=2 • Acute disease: absent=0; if present=2	Total score: 0=low risk 1=medium risk 2=high risk
MNA	Rating of six indicators (lowest score=positive risk): • Food intake decline: severe=0; moderate=1; none==2 • Weight loss: >3 kg=0; unsure=1; 1-3 kg=2; none=3 • Mobility: low=0; medium=1; independent=2 • Acute disease: yes=0; no=2 • Neuropsychological state: severe=0; mild=1; normal=2 • BMI (kg/m²): <19 =0; 19-<21=1; 21-<23=2; ≥23=2	Total score: 0-11 points=possible 12-14=no risk
NRS	Impaired nutritional status: • Absent (=0): normal nutritional status • Mild (=1): weight loss >5% in 3 months **Or** food intake below 50–75% of normal requirement in preceding week • Moderate (=2): weight loss >5% in 2 months **Or** BMI 18.5-20.5+impaired general condition **Or** food intake 25–50% of normal requirement in preceding week • Severe (=3): weight loss >5% in 1 month (>15% in 3 months) **Or** BMI <18.5+impaired general condition **Or** food intake 0–25% of normal requirement in preceding week Severity of disease: • Absent (=0): normal nutritional status • Mild (=1): hip fracture, chronic patients, (cirrhosis, COPD); chronic haemodialysis, diabetes, oncology • Moderate (=2): major abdominal surgery, stroke, severe pneumonia, hematologic malignancy • Severe (=3): head injury, bone marrow transplantation, ICU Age ≥70 (=1)	Total score: 0-2: none 3: light 4: moderate 5: severe

Table 1: *characteristics of three malnutrition screening tools. BMI, body mass index.*

Despite the importance of malnutrition on the fate of hospitalized patients, only two Chinese studies assessed the impact of malnutrition in older patients admitted to the hospital due to COVID-19 [40,41]. The study of Liu et al in Wuhan showed that one third (34%) of overweight patients with were at risk of malnutrition, and that NRS 2002 score correlated positively to the LOS and disease severity [40]. The study of Li at el in Beijing compared comorbidities in different nutritional risk groups of patients and showed more profound hypoalbuminaemia and anaemia associated with lymphopenia in patients with malnutrition. Still, both studies came from the same country (China), were monocentric by design, included a small number of patients (141 and 182 for Liu and Li, respectively), did not assess the effect of nutritional support, and did not conduct periodic re-evaluation of the nutritional status during hospitalisation. Hence, there is an evidence gap regarding the impact of nutritional status on outcomes among COVID-19 infected patients, and there is urgency in replicating the initial Chinese findings in other populations and settings. Also, and as of the 22nd of May, there is no study concerning the impact of nutritional management on COVID-19 infection outcomes.

2.2 Relation of the proposed project to ongoing research, to international initiatives and national and international collaboration

This project will build on a large national and international network of participating centres (hospitals) where cases of COVID-19 have been or are currently being admitted. All centres have collected information on nutritional status of the patients, which can be retrieved from EMR. To our knowledge, this will be the sole international network specifically focusing on the association between malnutrition and in-hospital outcomes of

COVID-19 patients. Currently, there are six Swiss, eight Portuguese, two Brazilian, one Canadian, one Israeli and one Iranian centres willing to participate; **Table 2** provides a short description of them. The fact that both Israeli and Iranian groups joined the consortium shows the importance of the research topic. Other centres in Portugal, Iran, Australia and Peru have been contacted. The proposed project is thus a large international collaboration.

Name	City	Country	Person of contact
Centre Hospitalier Universitaire Vaudois	Lausanne	Switzerland	Prof (10)(2e) Prof Peter Kopp
Hôpital Cantonal de Fribourg	Villars-sur-Glâne	Switzerland	Dr Anne-Catherine Barras-Moret
EOC - Mendrisio Regional Hospital. Beata Vergine	Mendrisio	Switzerland	Dr Piero Ossola Dr Massimo Quarenghi
Kantonsspital Aarau AG	Aarau	Switzerland	Prof Philipp Schuetz Prof Beat Müller
Kantonsspital St.Gallen	St Gallen	Switzerland	Dr Stefan Bilz
Luzerner Kantonsspital	Luzern	Switzerland	Dr Christoph Henzen
Hospital de São João	Porto	Portugal	Nutr Carla Galego
Hospital Lusíadas	Porto	Portugal	Nutr Luisa Trindade
ULSAM	Viana do Castelo	Portugal	Nutr Graça Ferro
Hospital do Divino Espírito Santo	Ponta Delgada	Portugal	Nutr Rita Carvalho
Hospital Garcia de Orta	Almada	Portugal	Nutr Anabela Almeida
Hospital Sousa Martins	Guarda	Portugal	Nutr Luis Matos
Centro Hospitalar de Leiria	Leiria	Portugal	Nutr Raquel Oliveira
Hospital Lisboa Norte (Santa Maria)	Lisboa	Portugal	Nur Patricia Nunes
Biobanque Québécoise de la COVID-19	Québec	Canada	Prof Vincent Mooser
Yazd University hospital	Yazd	Iran	Prof Masoud Mirzaei
Azrieli Faculty of Medicine	Safed	Israel	Prof. Milana Frenkel-Morgenstern
Hospital das Clínicas da FMUSP	São Paulo	Brazil	Prof Dan Waitzberg
Hospital das Clínicas de Porto Alegre	Porto Alegre	Brazil	Dr Beatriz Schaan

Table 2: *description of centres included in the network.*

Prof. (10)(2e), MD, Ph.D. is Associate Professor at the University of Lausanne. He was previously a professor of Nutrition and Public Health at the medical faculty of Lisbon, Portugal. He has a background in biochemistry, medicine and statistics and works in clinical research at the department of Internal Medicine of the Lausanne University Hospital (CHUV). He is one of the main researchers in nutritional epidemiology in Switzerland, having published over 50 papers on the topic in the last 5 years and initiated the first Swiss national nutritional survey in 2014. He has been active in the field of hospital malnutrition for 20 years, with several leading publications regarding the status of hospital malnutrition in Switzerland. Since 2007, he is investigator in the Colaus/PsyColaus study (www.colaus-psycolaus.ch), where he studies the associations between dietary intake and cardiovascular disease. In 2013 he received a grant from SNF to study the associations between dietary intake and socio-economic status in the Swiss population (grant 405940-145187, for PNR 69 "healthy nutrition"). The proposed project is thus a natural extension of the ongoing research of Prof. Marques-Vidal.

Peter Kopp is a Professor of Medicine and Adjunct Chief of the Division of Endocrinology, Diabetology and Metabolism at the University of Lausanne, Switzerland. Dr. Kopp obtained his MD degree and his training in Internal Medicine and Endocrinology at the University of Berne, Switzerland. In 1993, he moved to the United States for a research fellowship supported by a grant of the Swiss National Science Foundation at Northwestern University in Chicago. After 3 years, he joined the faculty at Northwestern and rose through the ranks to full professor. He has directed the Center for Genetic Medicine (CGM) at the Feinberg School of Medicine of

Northwestern University in Chicago from 2007 to 2014. In 2018, he has moved back to Switzerland to his current position. Dr. Kopp has extensive clinical experience in clinical endocrinology with a focus on thyroid cancer and thyroid dysfunction. His research is focusing on the molecular pathophysiology and genetics of thyroid and other endocrine disorders. In his collaborative work, he has also worked with several epidemiology groups focused on the CARDIA (Coronary Artery Risk Development in Young Adults) and MESA (Multi-Ethnic Study of Atherosclerosis) cohorts. From 2013 to 2019 he has served as the Editor-in-Chief of the journal Thyroid, an appointment that reflects his recognized expertise in clinical and basic thyroidology. He has been a member of the thyroid cancer guideline panel of the National Comprehensive Cancer Network since 2002. Dr. Kopp is an author or co-author of more than 190 publications, including chapters in major textbooks such as Harrison's Principles of Internal Medicine. In January 2020 he has been nominated as candidate for the presidency of the American Thyroid Association. He is responsible for Clinical Nutrition at the Lausanne University Hospital.

2.3 Description of the specific aims, the theoretical background and hypothesis, the approach and objectives, methods, milestones, expected results, and potential risks

Specific aims and objectives

Identify the relationship between nutritional status at hospital admission and in-hospital outcome of COVID-19 Infected patients. Study the impact of nutritional management during hospitalisation on in-hospital outcome. These aims will be split into different objectives and corresponding work packages, which will be described later:

1) Estimate the nutritional status of hospitalized COVID-19 infected patients (**WP2**)
2) Estimate the associations between nutritional status and admission to the Intensive Care Unit (ICU), the rate of intubation, the LOS and in-hospital mortality (**WP3**)
3) Describe the nutritional management of hospitalized COVID-19 infected patients (**WP4**)
4) Assess the impact of nutritional management on admission to the Intensive Care Unit (ICU), the rate of intubation, the LOS and in-hospital mortality (**WP5**)

Background and rationale

Malnutrition is a significant public health problem that prevails in the older adult population. Undernutrition is a proven risk factor of severe pneumonia whether is community acquired or nosocomial [42]. Several studies have shown that malnourished subjects with pneumonia have a higher rate of ICU admissions, longer hospital stays, and higher mortality rates [43]. These observations suggest that the nutritional status might also impact the severity and outcomes of COVID-19 infections. Given the limited data regarding the effect of malnutrition on outcomes of COVID-19 infected patients, an international, multicentre, adequately powered study is needed.

Hypotheses

Nutritional status/malnutrition increases the need for ICU admission, duration of ICU stay and hospitalization, and mortality among COVID-19 infected patients. Adequate management of malnourished COVID-19 infected patients will decrease LOS and in-hospital mortality.

Methods

The INCOVO study is a retrospective, international, multicentre study. All adult (≥18 years) patients with confirmed COVID-19 infection by validated methods and with a LOS ≥24 hours will be eligible. Patients will be identified from querying EMRs at the different study centres. All data are part of the clinical routine (**Table 3** next page). In the unfortunate but likely occurrence of a second COVID-19 wave, we expect all collaborating centres to implement their routine data collection. Indeed, the previous wave disrupted the routines of many hospitals and nutritional status could not be systematically assessed as usual. Hence, we expect that the knowledge and the procedures acquired during the first wave will be used to collect routine clinical data from all admitted COVID-19 patients. It should be noted that no extra data beyond those routinely collected within each collaborating centre would be obtained.

	Admission	In-hospital	Discharge
Age, sex	X		
Medical history/ comorbidities	X		
Prior drug therapy	X		
Height and weight	X		
Nutritional risk score	X	X	X
Nutritional support received	X	X	X
Albumin and/or prealbumin	X	X	X
Creatinine	X	X	X
C-reactive protein	X	X	X
Complete blood count	X	X	X
Liver function	X	X	X
Oxygen saturation	X	X	X
Outcomes (ICU, LOS, mortality)			X

Table 3: *core data set. ICU, intensive care unit; LOS, length of stay.*

Power analyses

Statistical power is conditioned on sample size. For some centres (i.e. Brazil and Canada), the admission of cases is still ongoing. It is expected that the Canadian register will contain information of 4,000 cases, and that the Brazilian hospitals (Hospital das Clínicas, one of the biggest in São Paulo, with a population of over 8 million, and Hospital das Clínicas de Porto Alegre, with a population of 1.5 million) will admit over 400 patients each. The CHUV has a register of 500 cases, the Portuguese centres will provide approximately 500 cases, and the Israeli group has data on 2200 cases. Based on existing data provided by the collaborating centres, a conservative sample size of 5,000 cases was used for simulations. We used an Excel-based tool [44] to calculate the power of a random-effects meta-analysis as defined previously [45]. The following parameters were used: average number of participants in each group: 10 to 100; number of centres: 5 to 25; heterogeneity: low (0.33) and high (3.0). Currently, there is no adequate effect size of malnutrition status on outcome of COVID-19 patients. We used the values for NRS-2002 from Liu et al [40]. A closer look at the results from table 4 and comparing to the results of table 1 suggests that the ORs are inverted (i.e. they correspond to patients not at risk). For instance, in case of influenza infection, the OR of malnutrition for death has been estimated at 25 [35], while the reported OR for severe disease by Liu et al is 0.103. We computed the beta coefficients from table 4 and estimated the ORs for patients at risk; the recalculated ORs were converted into Cohen's D as suggested [46] and used in the power calculations. In all cases, the power is above 90% (**Table 4**).

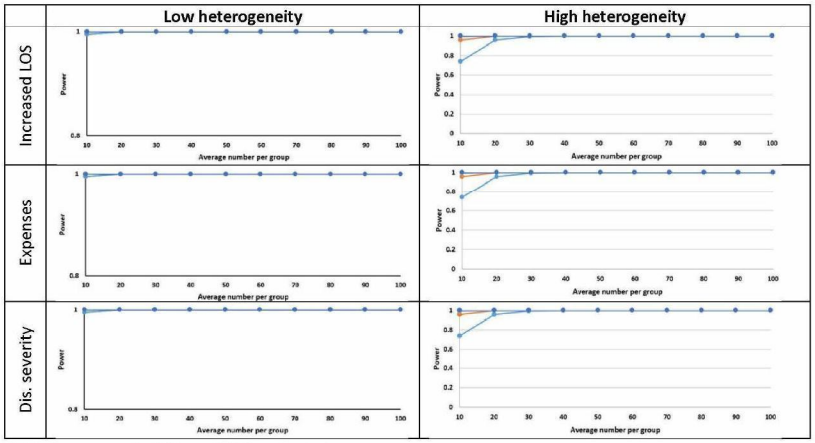

Table 4: *power calculations. LOS, length of stay.*

Statistical analyses

Statistical analyses will be conducted using Stata for windows (Stata corp, College Station, TX, USA) and R (The R Foundation for Statistical Computing). Two analytical levels will be implemented

- *In the first level*, codes aimed at importing/checking the data, creating the working database and analysing it will be provided for each collaborating group (see WP1 for details). Briefly, a first code will import the original Excel file containing the raw data and check it for consistency (i.e. ages <18 years or >110 years, extreme height or weight, or missing data). This first code will create the working dataset from the original one. For security reasons, data analysis will be performed on the working database, the original one being left untouched. The entire procedure is depicted in **Figure 2.**

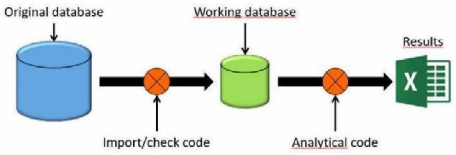

Figure 2: *procedure of data import, checking and analysis at the collaborating centres.*

A second code will then perform the analysis of the data. Descriptive results will be expressed as number of patients (percentage) for categorical variables and as median [interquartile range] or as mean±standard deviation for continuous variables. Comparison between outcomes will be performed by chi-square or Fisher's exact test for categorical variables and by student's t-test or Kruskal-Wallis test for continuous variables. The effect of malnutrition on outcomes will be assessed after multivariable adjustment using logistic regression, and the results will be provided as odds-ratio (OR) and 95% confidence interval. Multivariable models will be adjusted for relevant risk factors such as age, gender, body mass index or obesity, comorbidities (hypertension, diabetes, immune-suppression). All results will be either manually or automatically (tests ongoing) collected in an Excel file, which will be sent to the coordinating centre as indicated in WP1.

- *In the second level*, the data provided by the collaborating centres and obtained in the coordinating centre will be meta-analysed according to the different objectives indicated previously. The meta-analysis will be conducted at the coordinating centre in parallel by two persons (PMV and PostDoc) using two different statistical packages (Stata and R). This procedure allows cross-checking of results and reduces errors. Descriptive of each collaborating group patients' characteristics will be tabulated as performed in a previous multicentric study [47]. As we expect results to vary according to centre, results of the multivariable analyses will be meta-analysed using a random effects model. Results will be expressed in as effect size and 95% confidence interval, and depicted using forest plots. Outliers will be assessed using funnel plots and Egger's test. Validation of the findings will be performed by leave-one-out cross validation [48]. If necessary, a second round of analyses (i.e. by stratifying on a given risk factor) will be performed.

Work packages and expected results

WP0 - Obtaining authorization from ethics committees and directorates. Expected duration: 2-3 months. Main actors: Principal investigators of collaborating centres. Each participating centre will submit the project to its hospital directorate and local ethics committee. For Switzerland, the coordinating centre will do it on behalf of all other centres. The procedures may vary between countries, and experience suggests that a 3-months period is needed to obtain all authorizations. **Expected results:** authorizations to re-use the data.

WP1 - Data harmonization and common statistical analysis. Expected duration: 9 months. Main actors: Principal investigators, Post-Doctoral researcher, PIs of collaborating centres. The coordinating centre will communicate to each collaborating centre the minimal set of variables needed, plus their coding, via a standard operating procedure (SOP). Each centre will then extract the information from the electronic medical records and format it according to the SOP. In case of doubt (i.e. existence of several values for a single patient, differences in measuring units), the collaborating centres will contact the coordinators, and the SOPs will be updated accordingly. After data extraction and curation, each collaborating centre will transmit to the coordinating centre

a codebook detailing the characteristics of the database. The coordinating centre will then check all codebooks for consistency and eventually ask for clarification or modification. Once all datasets are harmonized, the statistical analysis can be performed. For consistency, two statistical packages have been retained: Stata (Stata corp., College Station, TX, USA) and R (The R Foundation for Statistical Computing). If necessary, SPSS or SAS could be supported. The coordinating centre will develop, test and distribute to the collaborating centres the statistical code needed to import and analyse the datasets according to the objectives of the study. Instructions on how to run the code will be consigned in a SOP. The collaborating centres will run the code and collect the results into specific forms (Excel); those forms will contain only aggregated data (i.e. averages, odds ratios and 95% confidence intervals, etc.). At any occasion, individual data will have to be transmitted to the coordinating centre. Upon completion, the forms will be sent to the coordinating centre as encrypted zip files; the passwords will be communicated to the coordinator by SMS (this procedure can be omitted if secured, encrypted email communication can be established between the collaborating centres and the coordinating centre). At arrival, the forms will be checked for completeness and any issue will be discussed with the collaborating centre via email. The complete, checked forms will then be uploaded into a common database for further meta-analysis. **Expected results**: two SOPs on data harmonization and data analysis; harmonized databases within all participating centres; harmonized data analysis, and database containing the metadata.

WP2: Estimate the nutritional status of hospitalized COVID-19 infected patients. Expected duration: 3 months. Main actors: Principal investigators, Post-Doctoral researcher, PIs of collaborating centres. Within each centre, the prevalence rates and 95% confidence intervals of malnourished patients will be assessed overall and according to gender and age group. The results will then be compiled as indicated in WP1. **Expected results**: one international, peer-reviewed publication, and several communications in local and international congresses.

WP3: Estimate the associations between nutritional status and admission to the Intensive Care Unit (ICU), the rate of intubation, the LOS and in-hospital mortality. Expected duration: 3-4 months. Main actors: Principal investigators, Post-Doctoral researcher, PIs of collaborating centres. Within each centre, the associations between malnutrition status (yes/no) and the different outcomes will be assessed using bivariate and multivariable methods. The results will then be compiled as indicated in WP1. **Expected results**: one international, peer-reviewed publication, and several communications in local and international congresses.

WP4: Describe the nutritional management of hospitalized COVID-19 infected patients. Expected duration: 3 months. Main actors: Principal investigators, Post-Doctoral researcher, PIs of collaborating centres. Within each centre, the different types of nutritional management (i.e. fractionated meals, oral nutritional support, enteral or parenteral nutrition) will be described, overall and stratifying on gender, age group, and ICU stay (yes/no). Results will be expressed as rates and 95% confidence intervals, and compiled as indicated in WP1. **Expected results**: one international, peer-reviewed publication, and several international communications.

WP5: Assess the impact of nutritional management on admission to the Intensive Care Unit (ICU), the rate of intubation, the LOS and in-hospital mortality. Expected duration: 3-4 months. Main actors: Principal investigators, Post-Doctoral researcher, PIs of collaborating centres. Within each centre, the associations between nutritional management (yes/no) and the different outcomes will be assessed using bivariate and multivariable methods. The results will then be compiled as indicated in WP1. **Expected results**: one international, peer-reviewed publication, and several communications in local and international congresses describing the beneficial impact of nutritional management on in-hospital outcomes.

Timelines and milestones

The entire study is projected to take 18 months, time for publication excluded. **Figure 3** next page displays the Gantt chart with the proposed timeline and milestones. Work packages 3 to 5 can be conducted almost in parallel if different writing groups are implemented. This would allow more time to solve any remaining issues. **Note:** this timeline does not take into account possible disruptions due to a second wave of COVID-19 infections.

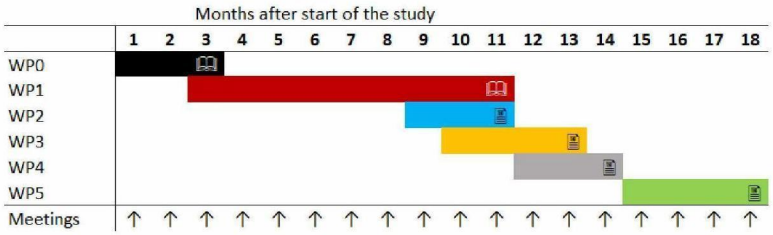

Figure 3: *proposed timeline and milestones. Please consult the text for information on the work packages.* 🕮 *denotes a standard operating procedure;* 🗎 *denotes a manuscript submitted for publication.*

Potential risks

The project relies on standard, routinely collected data already available at EMRs. The main risks are missing data due to the disruption of the clinical routines by the COVID-19 pandemic, and the occurrence of a second wave of the pandemic, which will likely halt all research activities as it was the case for Switzerland. Still, we believe that the large network of collaborating centres will provide enough data to conduct the study, and that in the case of a second wave most data management procedures can be conducted using telework.

Environmental risk: within-Switzerland travel will be done using public transport. Video meetings using Webex or Skype will be preferred. The carbon-related emissions of a 5-hour international video meeting including 4 participants range from 4 to 215 kg CO_2 [49]. Using such estimate for a 1-hour meeting of 20 participants and one monthly meeting, the carbon footprint of videoconferencing for the entire research period (18 months) will range between 72 and 3870 kg CO_2. This value was doubled to take into account the carbon cost of the data extraction and analysis (result: 144 to 7740 kg CO_2). The overall carbon footprint of the entire study thus seems reasonable.

2.4 Alignment of the proposed research project to the call priority areas

The goal of this study aligns perfectly with module 4 of the National Research Program NRP 78 "Clinical COVID-19 research and therapeutic interventions", as we will specifically identify the impact of nutritional status, and the possible benefits of an (early) nutritional intervention/therapy on outcomes of COVID-19 disease.

2.5 Potential impact of the research, i.e. rapid implementation, enabling early and valuable outcomes

Results will be submitted to gold open-access journals; if not possible, the green open access approach will be used. Authorship rules: collaborating centres will have two to three positions (if they participate actively in the writing group) or one position (if they do not). After acceptance of a paper, the coordinating centre will write a press report and validate it with the media office of the CHUV. The validated press report will be sent to selected media partners and to the collaborating centres for translation and dissemination in the local media. Other channels (centres' websites or Twitter) will also be used. The knowledge obtained by this study will implement the existing guidelines on COVID-19 nutritional management [35 50] by providing long-awaited evidence-based data.

We plan to increase the number of participating centres by inviting groups from other (non) European countries. We will use the research network to implement other research related to in-hospital malnutrition, namely: 1) the impact of obesity on outcomes of COVID-19 infected patients; 2) the impact of malnutrition on readmission rates of COVID-19 infected patients; and 3) specific studies, initiated by one collaborating group with the whole or part of the research network. The network could also be used for randomized controlled trials assessing the impact of early nutritional management of COVID-19 infected patients, provided further funding is obtained.

2.6 Bibliography / references

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