University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medicine

Improving clinical outcomes in critically ill COVID-19 patients

PhD thesis

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II. List of abbreviations

ALP: Alkaline phosphatase

APTT: Activated partial thromboplastin time

ATIII: Antithrombin III concentrate

biochem.: Clinical biochemistry

BUN: Blood urea nitrogen

CENTRAL: The Cochrane Central Register of Controlled Trials

CFS: Clinical Frailty Scale

CFT: Clot formation time

CI: Confidence interval

CK: Creatine kinase

CLI-30: Clot lysis index at 30 min

CLI-45: Clot lysis index at 45 min

Clin: Clinical

coag.: Conventional coagulation parameters

CRP: C-reactive protein

CT: Clotting time

CT: Computer tomography

CXR: Chest X-ray

ECA-test: Ecarin clotting assay test

EX-test: Extrinsic coagulation pathway test

FIB-test: Functional fibrinogen test

FIND: Frail Non-Disabled questionnaire

FiO2: Fraction of inspired oxygen

FiO2: Fraction of inspired oxygen.

FVIIa: Factor VIIa concentrate

FXIII: Factor XIII concentrate

GGT: Gamma-glutamyl transferase

GOT: Serum glutamic oxaloacetic transaminase

GPT: Serum glutamic pyruvic transaminase

HFRS: Hospital Frailty Risk Score

ICD: International Classification of Diseases

ICU: Intensive care unit

IL-6: Interleukin-6

IN-test: Intrinsic coagulation pathway test

infl.: Inflammatory parameters

INR: International normalized ratio

IQ: Interquartile

LDH: Lactate dehydrogenase

LOH: Length of hospitalization

LOT: Lysis onset time

LT: Lysis time

MCF: Maximum clot firmness

ML: Maximum lysis

MPI: Multidimensional Prognostic Index

n/a: Not available

n/r: No restriction

OR: Odds ratio

P/C: Prospective cohort

PAI-1: Plasminogen activator inhibitor-1

PCC: Prothrombin complex concentrate

PCR: Polymerase chain reaction

PECO: Patient, Exposure, Control, Outcome

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QUIPS: Quality in Prognosis Studies tool

R/C: Retrospective cohort

Rad: Radiological

rAT: Rapid antigen testing

rtPCR: Reverse transcription PCR

RVV-test: Russell's viper venom reagent test

SD: Standard deviation

SpO2: Peripheral capillary oxygen saturation

TPA-test: Tissue plasminogen activator test

TT: Thrombin time

UK: United Kingdom

VHA: Viscoelastic haemostasis assay

wbc: Whole blood count

WMD: Weighted mean difference

III. Scientific metrics

Number of publications **related to the subject** of the thesis:	2
Cumulative impact factor of publications related to the thesis:	11.0
D1: 1, Q1: 1, Q2: -, Q3: -, Q4: -	
Number of **total accepted/published** articles:	7
Cumulative impact factor of the published articles:	19.066
D1: -, Q1: 3, Q2: 2, Q3: -, Q4: -	
Number of total citations by **MTM2**:	119 independent
https://m2.mtmt.hu/api/author/10080576	
Hirsch Index:	5
Number of total citations by Google Scholar	158
https://scholar.google.hu/citations?hl=hu&user=sRKlE4UAAAAJ	
Hirsch Index:	5

IV. List of publications

Publications related to the subject of the thesis

Rottler M, Ocskay K, Sipos Z, Görbe A, Virág M, Hegyi P, Molnár T, Erőss B, Leiner T, Molnár Z. Clinical Frailty Scale (CFS) indicated frailty is associated with increased in-hospital and 30-day mortality in COVID-19 patients: a systematic review and meta-analysis. **Ann Intensive Care**. 2022 Feb 20;12(1):17. doi: 10.1186/s13613-021-00977-4. PMID: 35184215; PMCID: PMC8858439.
IF: 8.1; D1; original publication

Kovács EH, **Rottler M**, Dembrovszky F, Ocskay K, Szabó L, Hegyi P, Molnár Z, Tánczos K. Investigating the association between IL-6 antagonist therapy and blood coagulation in critically ill patients with COVID-19: a protocol for a prospective, observational, multicentre study. **BMJ Open**. 2022 Nov 4;12(11):e063856. doi: 10.1136/bmjopen-2022-063856. PMID: 36332964; PMCID: PMC9638747.
IF: 2.9; Q1; original publication

Publications not related to the subject of the thesis

Virág M, **Rottler M**, Gede N, Ocskay K, Leiner T, Tuba M, Ábrahám S, Farkas N, Hegyi P, Molnár Z. Goal-Directed Fluid Therapy Enhances Gastrointestinal Recovery after Laparoscopic Surgery: A Systematic Review and Meta-Analysis. **Journal of Personalized Medicine**. 2022; 12(5):734. https://doi.org/10.3390/jpm12050734
IF: 3.4; Q2; original publication

Leiner T, Nemeth D, Hegyi P, Ocskay K, Virag M, Kiss S, **Rottler M**, Vajda M, Varadi A, Molnar Z. Frailty and Emergency Surgery: Results of a Systematic Review and Meta-Analysis. **Front Med (Lausanne)**. 2022 Mar 31;9:811524. doi: 10.3389/fmed.2022.811524. PMID: 35433739; PMCID: PMC9008569.
IF: 3.9; Q1; original publication

Virág M, **Rottler M**, Ocskay K, Leiner T, Horváth B, Blanco DA, Vasquez A, Bucsi L, Sárkány Á, Molnár Z. Extracorporeal Cytokine Removal in Critically Ill COVID-19 Patients: A Case

Series. **Front Med (Lausanne)**. 2021 Nov 19;8:760435. doi: 10.3389/fmed.2021.760435. PMID: 34869464; PMCID: PMC8639689.
IF: 5.058; Q1; original publication

Virág M, Leiner T, **Rottler M**, Ocskay K, Molnar Z. Individualized Hemodynamic Management in Sepsis. **J Pers Med**. 2021 Feb 23;11(2):157. doi: 10.3390/jpm11020157. PMID: 33672267; PMCID: PMC7926902.
IF: 3.508; Q2; knowledge publication

Szabó GV, Szigetváry C, Szabó L, Dembrovszky F, **Rottler M**, Ocskay K, Madzsar S, Hegyi P, Molnár Z. Point-of-care ultrasound improves clinical outcomes in patients with acute onset dyspnea: a systematic review and meta-analysis. **Intern Emerg Med**. 2023 Mar;18(2):639-653. doi: 10.1007/s11739-022-03126-2. Epub 2022 Oct 31. PMID: 36310302; PMCID: PMC10017566.
IF 3.2; Q1; original publication

V. Introduction

V.1. Emergence of SARS-CoV-2 and the global pandemic

In late 2019, health officials reported an outbreak of atypical pneumonia in Wuhan, China. Subsequently, a novel coronavirus was identified as causative pathogen, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The virus presented unique epidemiological and clinical features which enabled it to cause the most consequential pandemic in recent history, officially named by the World Health Organization as coronavirus disease 19 (COVID-19). SARS-CoV-2 transmission between humans appeared during asymptomatic or pre-symptomatic phases further enhancing the rapid spread across continents [2]. By the end of 2020 several millions of cases had been confirmed, and consequently, an extensive increase in mortality was seen worldwide [3].

V.2. Impact on healthcare systems

The pandemic imposed unprecedented strain on healthcare systems. Due to the overwhelming number of critically ill patients with respiratory failure, intensive care units reached soon enough maximum capacity [4]. Among others, the shortage of healthcare personnel, protective gear, and technical equipment, such as ventilators, extracorporeal membrane oxygenation (ECMO) devices, and dialysis machines, became limiting factors for treatment, even in well-resourced healthcare infrastructures. Disparities in these resources between regions and countries further intensified the inequalities in the quality of care observed during the pandemic [5]. The overwhelming numbers of patients, together with a scarcity of healthcare capacity, had a significant effect on mortality rates [6].

Patients with COVID-19 showed a broad range of clinical outcomes from individuals without any symptoms up to critically ill patients suffering from severe pneumonia with hypoxemic respiratory failure, and even multiple organ failure resulting in death. The outcomes in the critically ill population were affected by various factors including age, existing chronic diseases, and frailty alongside the individual patients' immune response. There has been a great scientific effort to identify and validate such prognostic factors, so that, patients most suitable for intensive care, could be allocated correctly [7]. Fair and ethical allocation to adequate levels of care, thus, became of utmost importance in providing for the most severely ill [8]. Using risk

stratification tools for protocolized admission and determining the ceiling of care could help the decision-making and create transparency in these uncertain times.

V.3. Risk factors of severe COVID-19

An increasing body of epidemiological data identified several risk factors for progression to severe disease and mortality: advanced age, male sex, frailty, and comorbid conditions such as cardiovascular disease, diabetes mellitus, obesity, chronic kidney disease, and chronic respiratory disorders increased the odds for adverse outcomes [9-11]. In large cohort studies patients aged over 65 years were disproportionately affected, and had significantly higher chances of hospitalization, critical illness, and mortality as compared to a younger population [10]. Moreover, mortality rates have steeply risen with advancing age [12].

However, chronological age alone does not fully explain poor outcomes, nor should it be the sole criterion for clinical decision-making.

V.4. Frailty

Clinical decisions regarding advance care planning, should be guided by biological vulnerability and individual health status rather than age alone. A well-established concept to describe this age-independent, biological vulnerability of an individual is frailty [13].

Frailty describes a state of reduced physical, physiologic and cognitive reserve as a consequence of an ongoing accumulation of various deficits through time leading to increased vulnerability to stressors [14]. Although frailty is linked to ageing, progression in every individual is distinct. Nevertheless, evidence from studies preceding the COVID-19 pandemic, demonstrated that frailty is an age independent risk factor of mortality, particularly in the elderly intensive care unit (ICU) population. A systematic review from 2017 by Muscedere et al. indicated that a pooled prevalence of frailty among ICU patients was 30%. Frail ICU patients had higher hospital and long-term mortality, as well as lower rates of discharge to home [15]. Consequently, frailty assessment has been widely advocated to be included in prognostic evaluations and triaging of ICU patients in several pre-pandemic studies [15-17].

Apparently, in the surge of the pandemic, there was an urge to measure frailty within the scope of a risk stratification tool. Nevertheless, its use in these exceptional circumstances—triaging patients due to a shortage of ICU capacity—remains unvalidated and lacks scientific evidence to support its justification or effectiveness.

V.5. Pathophysiological and clinical advances

The SARS-CoV-2 virus showed hazardous pathophysiologic properties, that were mostly unknown at the time of its first appearance. Host immune response dysregulations, along with its effect on multiple organ systems led to alarmingly high mortality rates during the pandemic's initial stages. Early clinical management consisted mainly of empirical approaches and low quality evidence from small uncontrolled studies, that later on proved ineffective [18]. As time passed high-quality evidence through large adaptive randomized controlled platform trials surfaced. These trials, such as RECOVERY and REMAP-CAP, for example, identified the benefit of low-dose dexamethasone, which reduced mortality in patients requiring supplemental oxygen or mechanical ventilation [19]. In parallel, significant advances were made in understanding the pathophysiological effects of SARS-CoV-2. The recognition of hyperinflammation and immune dysregulation as key drivers of severe disease facilitated the implementation of immunomodulatory therapies, such as tocilizumab, a monoclonal antibody targeting the interleukin 6 (IL-6) receptor. The survival benefit associated with tocilizumab has been demonstrated in both pivotal clinical trials [20, 21].

From a pathophysiological perspective, the hyperinflammatory and dysregulated immune response activates both the inflammatory and the coagulation cascades, directly by inflammatory mediators and indirectly via endothelial cell injury. This interplay between inflammation and coagulation is commonly referred to as thomboinflammation [22]. These mechanisms altogether contribute to the imbalance of the haemostasis that is characterised by a procoagulant state. Even despite the implementation of thromboprophylaxis, an increased number of thrombotic complications have been described [23]. Moreover, in critically ill COVID-19 patients, the procoagulant state cannot be effectively mitigated by higher intensity anticoagulation without counteracting its benefits by simultaneously increasing the risk of bleeding [24, 25]. One of the proinflammatory cytokines that has a key role in the crosstalk between the immune system and blood coagulation is IL-6 [26].

The introduction of IL-6 receptor antagonists into the treatment protocol of critically ill COVID-19 patients, prompted by the favourable outcomes of the aforementioned trials, has given rise to additional questions. In particular, it remains unclear whether these immunomodulatory agents have an effect on the hypercoagulable state in severe COVID-19, and if so, how they modulate coagulation and fibrinolysis.

VI. Objectives

This thesis seeks to contribute to the growing body of knowledge accumulated during the challenging circumstances of the COVID-19 pandemic, which placed an extraordinary strain on healthcare systems, particularly on intensive care. Its objectives are not only to improve clinical outcomes in COVID-19 but also to help prepare for future pandemics through advances in evidence-based medicine.

In order to achieve these objectives, the work is twofold:

- First, we conducted a systematic review and meta-analysis to investigate the association of frailty and clinical outcomes and thereby help guide macro-level healthcare decision-making and resource allocation.

- Second, we developed a protocol for a prospective, observational multicentre trial to further explore the effects of IL-6 antagonists on the coagulation system. This aims to enhance our understanding on the micro-level, pathophysiologic mechanisms of thromboinflammation.

VII. Methods: The studies

VII.1. Clinical Frailty Scale (CFS) indicated frailty is associated with increased in-hospital and 30-day mortality in COVID-19 patients: a systematic review and meta-analysis

VII.1.1. Introduction

Frailty is a state characterized by decreased physiologic reserve, leading to increased vulnerability following a stress. As a result, frail individuals are at higher risk of adverse health outcomes after an incident of any origin, compared to non-frail individuals of the same age. This is due to their diminished capacity to restore homeostasis. It appears to be a consequence of an ongoing accumulation of deficits throughout the lifespan. However, it is important to emphasize, that the rate at which deficits accumulate varies considerably among individuals—in frailty the decline in physiologic reserve is accelerated. This is mostly influenced by genetic, environmental, and lifestyle factors [13, 14]. Apparently, the measurement of frailty has become increasingly important for risk stratification. Numerous methods have been described to characterize frailty. Certainly, this makes frailty assessment somewhat heterogenous and complicated for comparison across studies.

The *Clinical Frailty Scale (CFS)* was created by Rockwood et al. in 2005 to provide a simple approach with good predictive value [27]. The original 7-point scale was later upgraded to 9-levels which covered: “very fit” (1), “fit” (2), “managing well” (3), “living with very mild frailty” (4), “living with mild frailty” (5), “living with moderate frailty” (6), “living with severe frailty” (7), “living with very severe frailty” (8), “terminally ill” (9); *(Figure 1)* [28]. The score assesses different levels of functional independence, through items that can be observed by anyone. These include mobility, balance, use of walking aids, and the ability to perform activities of daily living, independently. [28] Thus, integrating a progressive accumulation of morbidity, loss of physical and cognitive function in a joint phenotype. It is meant to reflect a baseline health state in at least two weeks before the onset of an acute condition. The CFS is widely used in different clinical settings [29]. CFS outperformed the Charlson comorbidity index and age in predicting in-hospital mortality of patients older than 75 years with emergency hospital admission [30] and is an independent predictor of short- and long-term mortality in patients over 70 admitted to the ICU [31].

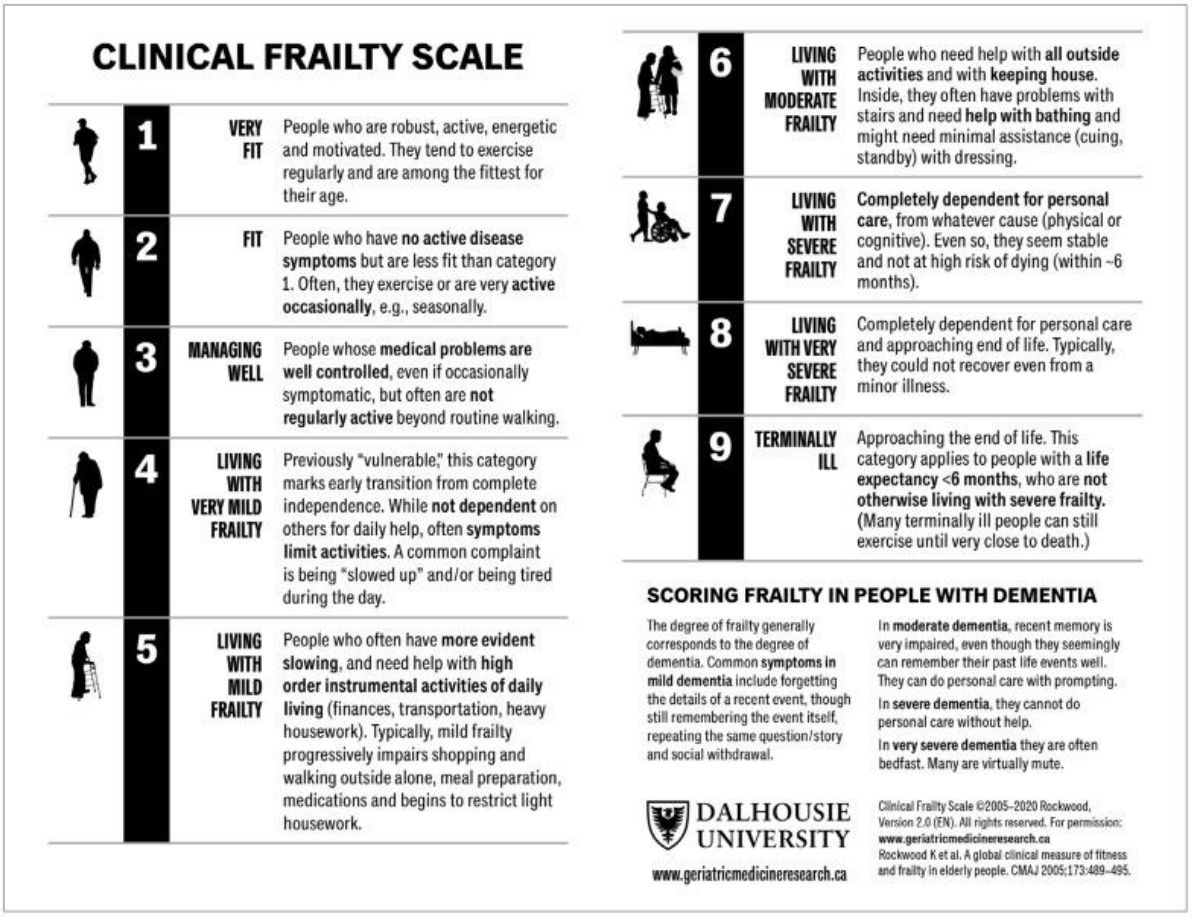

Figure 1: The Clinical Frailty Scale: *Assessment of different levels of frailty. (Rockwood et al., 2020; [28]).*

The *Hospital Frailty Risk Score (HFRS)* was developed to assess risk of frailty in older individuals automatically from routinely collected data using the International Classification of Diseases version 10 (ICD-10) codes [32]. On the one hand it is a useful tool for research and sociodemographic observations, on the other hand it has a potential for implementation into an automated hospital electronic system for acute clinical risk stratification [32].

The *Multidimensional Prognostic Index (MPI)* was developed as a prognostic tool for elderly patients. It is mainly used in the geriatrics as a part of a comprehensive geriatric assessment process. It has been validated for short-term and long-term outcomes alike and is not only meant as a tool for risk stratification, but also to enhance geriatric care by aiding to target specific interventions, thus improving outcomes [33]. Although it is a valuable tool in geriatric management, but its usefulness is limited in other fields and especially in critical care.

Frailty assessment was adopted in many guidelines in the triage of COVID-19 patients to aid decision-making regarding intensive care admission or the commencement of mechanical

ventilation [34]. Recent studies and a meta-analyses reported higher odds and hazard ratios for mortality in frail COVID-19 patients [35-42].

We aimed to provide a detailed summary on the use of frailty tools in COVID-19, assessing the odds of patients with frailty for in-hospital and 30-day mortality, ICU admission, and length of hospitalization (LOH).

VII.1.2. Methods

VII.1.2.1. Protocol registration and reporting

The protocol was prospectively registered via PROSPERO under Registration number CRD42021241544. There was no deviation from the protocol. We report our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [43] (Additional file 2, online supplementary material; see chapter VII.1.2.7).

VII.1.2.2. Eligibility and definitions

We formulated our clinical question using the PECO format. Based on preliminary searches, we chose to use two PECOs. We selected studies reporting on adult hospitalized patients with COVID-19, comparing frail (or frailer) patients to not frail (or less frail) patients. The assessed outcomes were all-cause in-hospital and 30-day mortality, ICU admission, and LOH. In our other analysis, the average frailty score of deceased COVID-19 patients was compared to survivors'.

COVID-19 positivity was defined as clinical, radiological, or laboratory diagnosis [44]. Any validated frailty scores and indexes were included, as well as non-validated ones, if the record contained sufficient information on the used index.

Studies with original data reporting on at least ten patients were eligible independently of study design. Abstracts and full-texts were both accepted.

VII.1.2.3. Search and selection

We searched MEDLINE (via PubMed), EMBASE, Scopus, The Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science on the 24th of September 2021 for eligible articles. We used "Title, Abstract, Keywords" filter in Scopus. No other filters or

restrictions were applied. We also scanned the reference lists of the included studies and their citations in Google Scholar. The following search key was used: ("covid 19" OR "Wuhan virus" OR coronavirus OR "2019 nCoV" OR SARS-cov-2) AND frail*.

After removing duplicates using a reference management software (EndNote X9, Clarivate Analytics), two review authors independently screened titles, abstracts, and then full texts against predefined eligibility criteria. Discrepancies were resolved by a third review author. Inter-rater reliability was determined at every phase by Cohen's kappa coefficient, where values 0.01–0.20 indicate slight, 0.21–0.40 indicate fair, 0.41–0.60 indicate moderate, 0.61–0.80 indicate substantial and 0.81–1.00 indicate almost perfect or perfect agreement, respectively [45].

Outcomes reported by at least three studies using the same frailty score comparing identical frailty subgroups were included in the meta-analysis. All other eligible studies were incorporated into the qualitative synthesis.

VII.1.2.4. Data collection

Data on the first author, publication year, countries, study design, number of patients in each comparison group, their baseline characteristics (sex, age), type of frailty score used, method of frailty assessment, training of the assessor and available primary and secondary outcome parameters were extracted by two independent review authors in duplicate using our standardized data collection form in Microsoft Excel. Disagreements were resolved by a third independent investigator. Data from studies reporting individual patient data or raw data were regrouped if statistically feasible. Overlapping populations were identified, and the study with the largest sample size was included in the analyses.

VII.1.2.5. Risk of bias

Following the recommendations of the Cochrane Collaboration, the Quality in Prognosis Studies (QUIPS) tool was used by two authors independently [46]. Disagreements were resolved by a third author. In the study participation domain, gender, age, ethnicity, and comorbidities were taken into account. Study attrition was not judged for retrospective studies. In the prognostic factor measurement domain, the specification of the frailty assessor, information about their training, and missing data on frailty were considered. Less than 10% missing data were considered low risk, 10–20% some concerns, and more than 20% resulted in

high risk for the whole domain. Outcome measurement and statistical analysis domains carried low risk in most cases because mortality is an objective outcome, and we mostly used crude numbers of patients reported by the authors. In the case of ICU admission, a detailed protocol for ICU admission was needed. In the study confounding domain, studies separately reporting baseline information for the frailty groups were judged low risk if no clinically significant differences were seen, some concerns if some differences were seen, and high risk if no data was reported. The overall risk of bias was calculated using the suggestions of Grooten et al. [47].

VII.1.2.6. Statistical analysis

Our primary aim was to investigate the differences between the two groups (Frail group vs Not frail group). We only included studies using the same cutoff in each analysis; therefore, multiple analyses were performed with slightly different frailty cutoffs. Most eligible studies used arbitrary categorization and grouping of patients by frailty, therefore we ought to perform multiple analyses (e.g. CFS 1–3 vs 4–9; 1–4 vs 5–9; 1–5 vs 6–9).

For dichotomous outcomes, odds ratios (ORs) with their 95% confidence intervals (CI) were calculated from the original raw data of the articles. In some cases, crude ORs were extracted and pooled with the calculated ORs. For continuous outcomes, weighted mean differences (WMDs) with 95% CI were calculated from the original raw data of the articles except in some cases when standard deviations (SDs) and means were calculated from the first quartile, median, the third quartile, and sample size according to Wan's method [48].

We used the random effect model by DerSimonian and Laird [49]. We estimated the heterogeneity using the χ^2 test with a significance of $p < 0.1$ and the I^2 indicator. We followed the Cochrane Handbook's recommendations when interpreting heterogeneity (http://handbook.cochrane.org, Chapter 10), meaning that I^2 values between 30 and 60% were considered as moderate heterogeneity, between 50 and 90% as substantial heterogeneity and as considerable heterogeneity above 75%. Results of each meta-analysis were displayed graphically using forest plots.

Subgroup analyses were performed in the analyses of mortality associated with CFS, where the subgroups were determined by country (United Kingdom; UK and non-UK), by age (older than 65 years and no age restriction), and by mortality (in-hospital mortality and 30-day mortality). In the case of ICU admission CFS 1–3 vs 4–9, we performed a subgroup analysis, where groups were determined by frailty-based decision making.

To determine the robustness of an assessment, we performed the leave-one-out sensitivity analysis for all outcomes when reasonable. Using this method, we could examine whether altering any assumptions may lead to different final interpretations or conclusions [50]. The potential for a "small study effect", including publication bias, was examined by visual inspection of funnel plots. Furthermore, Egger's test was performed for analyses including at least ten studies to indicate significant asymmetry by using a significance of $p < 0.05$.

All data management and statistical analyses were performed with Stata (version 16.0, StataCorp).

VII.1.2.7. Supplementary material

The online supplementary material can be found at:

- https://static-content.springer.com/esm/art%3A10.1186%2Fs13613-021-00977-4/MediaObjects/13613_2021_977_MOESM1_ESM.pdf
- https://static-content.springer.com/esm/art%3A10.1186%2Fs13613-021-00977-4/MediaObjects/13613_2021_977_MOESM2_ESM.docx

VII.1.3. Results

VII.1.3.1. Selection and characteristics of included studies

The systematic search yielded 3640 records. After duplicate removal, 1487 records were screened by title, 550 by abstract, and 331 by full text. 54 studies were included in the qualitative and 42 in the quantitative synthesis. The detailed selection process and Cohen's kappa values are shown in *Fig. 2*.

The most important aspects of each included study are presented in *Table 1*. Only cohort studies were enrolled. Of the 54 studies, 10 collected data prospectively, 46 used the CFS, two the HFRS, two both, three the MPI, two studies a modified frailty index (mFI), and one the Frail Non-Disabled (FiND) questionnaire. All studies included patients from a clinical setting. Most studies enrolled patients over 65 years.

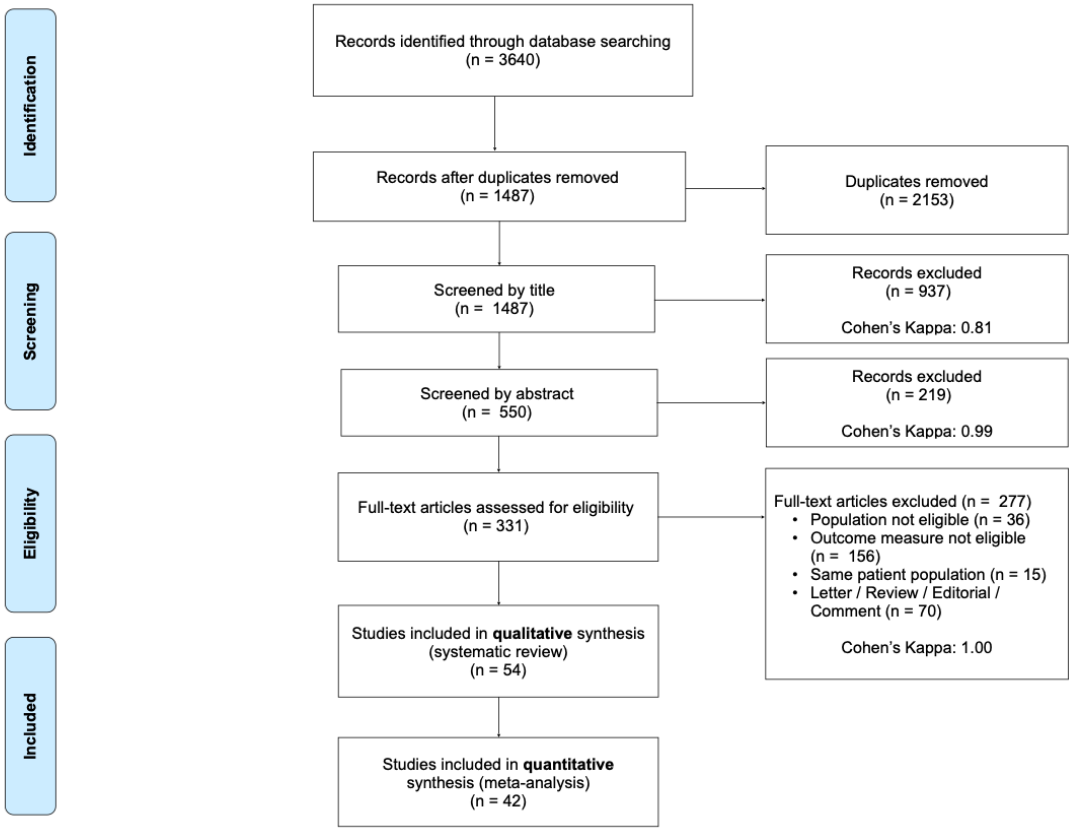

Figure 2: Flowchart of study selection *according to the PRISMA Statement*

VII.1.3.2. Risk of bias

Risk of bias was assessed separately for in-hospital and 30-day mortality, difference in frailty score for in-hospital and 30-day mortality, ICU admission, and LOH. Most studies did not report detailed baseline data for the frailty groups, therefore carried a high risk of bias (Additional file 1: Fig. S1–S6, online supplementary material; see chapter VII.1.2.7).

VII.1.3.3. Frailty is associated with an increased chance of mortality

Frailty measured with the Clinical Frailty Scale

46 studies reported on CFS as a measure of frailty. The investigated cohort was dominated by patients from the United Kingdom (UK) in 20 included studies. Most studies reported on in-hospital mortality. Since the CFS represents a continuous spectrum, without evidence for definitive cutoff values, most included studies showed arbitrary partitioning of the CFS. Therefore, we sought to perform quantitative analyses with three distinct partitions (CFS 1–3 vs 4–9, CFS 1–4 vs 5–9, CFS 1–5 vs 6–9). In each of these divisions we performed three different subgroup analyses. Given that a substantial number of patients were from the UK, we divided studies from the UK versus studies outside the UK. Furthermore, the CFS was only validated for patients older than 65 years; we grouped studies accordingly, whether they included patients below 65 years or not. It is important to note that although there was no age restriction at inclusion in some studies, most patients were older than 65 years of age. Beyond that, to further evaluate statistical homogeneity we also undertook a subgroup analysis of assessed mortality (in-hospital vs 30 days). All analyses indicated significant results.

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
Aliberti, M. J. R. et al. (2020) [51]	Brazil	30.03.2020. – 07.07.2020	R/C	CFS	R/P+	>50y	PCR	1830	666	66	59-74	1061 (38)	30-day mortality
Andrés-Esteban, E. M. et al. (2021) [52]	Spain	15.07.2020 - 31.07.2020	R/C	CFS	R/P+	0-97	PCR	254	104	70.16	16,01	155 (61)	in-hospital mortality; frailty diff. for in-hospital mort.; ICU admission; LOH
Apea, V. J. (2021) [53]	UK	01.01.2020 – 13.05.2020	P/C	CFS, HFRS	R	> 16	PCR	831	315	n/a	n/a	n/a	30-day mortality
Aw, D. (2020) [54]	UK	01.03.2020 – 30.04.2020	R/C	CFS	R/P+	> 65	PCR or Clin or Rad	677	271	81.1	8.1	366 (54.1)	in-hospital mortality, ICU admission
Baker, K. F. et al. (2021) [55]	UK	31.01.2020 - 16.04.2020	R/C	CFS	R	>18y	PCR	316	84	75	60-83	173 (54.7)	frailty diff. for 30-day mort.
Bavaro, D. F. et al. (2021) [56]	Italy	01.03.2020 - 15.06.2020	R/C	CFS	R/P+	>65y	PCR	206	56	80	72-86	98 (48)	in-hospital mortality; LOH
Bielza, R. (2021) [57]	Spain	20.03.2020 – 01.06.2020	R/C	CFS	P+	> 70	PCR or Clin	630	282	87	82.9-91.1	223 (35.4)	30-day mortality, frailty diff. for 30-day mort. and severe vs non-severe cases
Blomaard, L. C. (2021) [58]	Netherlands	27.02.2020 – 14.05.2020	R/C	CFS	R/P+	> 70	PCR or Clin or Rad	1376	499	78	74-84	830 (60.4)	in-hospital mortality, ICU admission, LOH, invasive ventilation, delirium, discharge destination

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
Bradley, P. (2020) [59]	UK	01.04.2020 – 14.04.2020	P/C	CFS	P	n/r	PCR	830	300	70	58-80	509 (61.3)	30day mortality, frailty diff. for 30-day mortality and 72 h mortality
Brill, S. E. (2020) [60]	UK	10.03.2020 – 08.04.2020	R/C	CFS	P	n/r	PCR	450	173	72	56-83	272 (60)	frailty diff. for in-hospital mortality
Burns, G. P. (2020) [61]	UK	13.03.2020 – 22.04.2020	R/C	CFS	P	n/r	PCR	28	14	81.5	54-91	15 (54)	in-hospital mortality; frailty diff. for in-hospital mortality and duration of respiratory support
Cecchini, S. et al. (2021) **[62]**	Italy	01.03.2020 - 30.04.2020	R/C	CFS	R	>65y	PCR/ CXR	122		87,1	6	55 (45.1)	frailty diff. for in-hospital mort
Chinnadurai, R. (2020) [63]	UK	13.03.2020 – 30.04.2020	R/C	CFS	P	n/r	PCR	215	86	74	60-82	133 (61.9)	in-hospital mortality
Covino, M. et al. (2021) [64]	Italy	01.0.4.2020 - 30.03.2021	P/C	CFS	P	>80y	PCR	729	287	85	82-89	345 (47.3)	in-hospital mortality
Cuvelier, C. et al. (2021) **[65]**	Switzerland	13.03.2020 - 11.05.2020	R/C	CFS	R	>80y	NR	20	10	87,1	82,8-90,6	14 (70)	frailty diff. for in-hospital mort
Davis, P., R. (2020) [66]	UK	18.03.2020 – 20.04.2020	R/C	CFS	R	n/r	PCR	222	95	82	56-99	74 (33)	30-day mortality
De Smet, R. (2020) [67]	Belgium	12.03.2020 – 30.04.2020	R/C	CFS	P+	n/r	PCR	81	19	85	81-90	33 (41)	in-hospital mortality, frailty diff. for in-hospital mortality
Dres, M. et al. (2021) [68]	France, Switzerland, Belgium	25.02.2020 - 04.05.2020	P/C	CFS	P	>70y	PCR	1199	442	74	71-77	873 (72.8)	30-day mortality
Fagard K. (2021) [69]	Belgium	16.03.2020 – 16.05.2020	R/C	CFS	P+	> 70	PCR or Clin and CT	105	14	82	76-87	55 (52.4)	in-hospital mortality, frailty diff.

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
													for in-hospital mortality
Fallon, A. et al. (2021) **[70]**	Ireland	25.03.2020 - 24.04.2020	R/C	CFS	R/P+	>65y	PCR	86	29	77		n/r	frailty diff. for 30-day mort.
Fumagalli, C. et al. (2021) **[71]**	Italy	22.02.2020 - 30.05.2020	R/C	mFI	R	>75y	Clin	221	97	82	78-86	134 (60.6)	in-hospital mortality
Gilis, M. (2020) [72]	France	03.03.2020 – 25.04.2020	P/C	CFS	P	> 75	PCR	186	56	85.3	5.78	92 (49.5)	30-day mortality, ICU admission, laboratory findings, symptoms, delirium, treatment
Hewitt, J. (2020) [73]	UK, Italy	27.02.2020 – 28.04.2020	P/C	CFS	P+	> 18	PCR or Clin	1564	425	74	61-83	903 (57.7)	in-hospital mortality; LOH
Hoek, R. A. S. (2020) [74]	Netherland	27.02.2020 – 30.04.2020	R/C	CFS	R	n/r	PCR	23	5	n/a	n/a	18 (78.3)	frailty diff. for in-hospital mortality (solid organ transplant recipients)
Jung, C. et al. (2021) [75]	Austria, Belgium, Denmark, Egypt, England, France, Germany, Greece, India, Iran, Iraq, Ireland, Israel, Italy, Libya, Mexico, Morocco, Netherland, Norway, Poland, Portugal, Saudi	19.03.2020 - 26.05.2020	P/C	CFS	P+	>70y	PCR	1346	540	75	72-78	965 (71.7)	30-day mortality

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
	Arabia, Spain, Sudan, Switzerland, USA												
Knights, H. (2020) [76]	UK	01.03.2020 – 31.03.2020	R/C	CFS	R	n/r	PCR	108	34	68.7	1.5	63 (58)	frailty diff. for in-hospital mortality
Koduri, G. et al. (2021) **[77]**	UK	20.02.2020 - 07.05.2020	R/C	CFS	R	>18y	PCR or Clin+CT	500	193	69,39	17,2	300 (60)	frailty diff. for in-hospital mort.
Kundi, H. (2020) [78]	Turkey	11.03.2020 – 22.06.2020	R/C	HFRS	R	> 65	PCR	18234	3315	74.1	7.4	8498 (46.6)	in-hospital mortality; frailty diff. for in-hospital mortality; LOH
Kurtz, P. et al. (2021) **[79]**	Brazil	27.02.2020 - 28.10.2020	P/C	mFI	P	>18y	PCR	13301	1785	54	41-69	7752 (58)	30-day mortality
Lozano-Montoya, I. et al. (2021) [80]	Spain	03.2020 - 05.2020	R/C	CFS	R	>75y	PCR or Clin+CT	300	111	86,3	6,6	112 (37.3)	in-hospital mortality
Maguire, D. et al. (2021) **[81]**	UK	18.05.2020 - 06.07.2020	R/C	CFS	n/r	>16y	PCR	261	58			119 (46)	30-day mortality
Maki, Y. et al. (2021) [82]	Japan	02.2020 - 05.2020	R/C	MPI	R	>65y	PCR	18	4	82,89	10,2	7 (38.9)	in-hospital mortality
Marengoni, A. (2020) [83]	Italy	08.03.2020 – 17.04.2020	R/C	CFS	R	n/r	PCR or CT	165	42	69.3	14.5	100 (60.6)	in-hospital mortality, ICU admission
McWilliams, D. (2021) [84]	UK	03.2020 – 04.2020	P/C	CFS	P	> 18	n/a	177	67	n/a	n/a	127 (71.8)	in-hospital mortality, ICU mortality, ICU rehabilitation (only ICU patients)
Mendes, A. (2020) [85]	Switzerland	13.03.2020 – 14.04.2020	R/C	CFS	R	> 65	PCR or Clin and Rad	235	76	86.3	6.5	102 (43.4)	in-hospital mortality, frailty diff.

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
													for in-hospital mortality
Moledina, S. M. (2020) [86]	UK	23.03.2020 – 07.04.2020	R/C	CFS	R	n/r	PCR	229	75	73	56-81	144 (63)	frailty diff. for 30-day mortality
Moloney, E (2020) [87]	Ireland	17.02.2020 – 24.04.2020	R/C	CFS	R	> 70	PCR	69	16	79	75-85	40	in-hospital mortality; symptoms, COVID-19 severity, radiological findings, ventilation
Navaratnam, A. V. et al. (2021) [88]	UK	01.03.2020 - 31.05.2020	R/C	HFRS	R	>18y	PCR	91541	28200			50668 (55.4)	in-hospital mortality
Noble, J. H. Et al. (2021) [89]	UK	03.2020 - 06.2020	R/C	CFS	n/r	>18y	PCR or Clin	164	68	62,1		110 (61.1)	in-hospital mortality
Osuafor C.N. (2021) [90]	UK	01.03.2020 – 15.05.2020	R/C	CFS	R	> 65	PCR or Clin	214	74	80.3	8.3	120 (56.1)	in-hospital mortality, ICU admission, LOH, readmission; delirium, mobility at discharge, prolonged LOH, death within 14 days of discharge
Owen, R. K. (2020) [91]	UK	29.02.2020 – 16.04.2020	R/C	CFS	R	> 65	PCR	206	92	78.8	8.3	n/a	30-day mortality, ICU admission, ICU mortality
Piers, R. (2021) [92]	Belgium	03.2020 – 04.2020	R/C	CFS	R	> 80	n/a	711	246	n/a	n/a	n/a	in-hospital mortality, ICU admission

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
Pilotto, A. et al. (2021) [93]	Italy	31.01.2020 - 31.12.2020	P/C	MPI	P	>65y	PCR	227	43	80,5		93 (41)	in-hospital mortality
Ponsford, M. J. et al. (2021) [94]	UK	01.03.2020 - 01.07.2020	R/C	CFS	P	>18y	PCR	2508	885	74	62,5-85,5	1363 (54.3)	in-hospital mortality
Ramos-Rincon, J. M. Et al (2021) [95]	Spain	03.03.2020 - 02.05.2020	R/C	CFS, HFRS	R	>18y	PCR	290	48				in-hospital mortality; ICU admission; LOH
Sablerolles, R. S. G. et al. (2021) [96]	Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Switzerland, UK	30.03.2020 - 15.07.2020	R/C	CFS	P	>18y	PCR or Clin+ CT	2434	456	67	55-77	1480 (61)	in-hospital mortality;ICU admission
Steinmeyer, Z. (2020) [97]	France	13.03.2020 – 04.05.2020	R/C	FIND	R	n/r	PCR or Clin and CT	94	17	85.5	7.5	42 (44.6)	in-hospital mortality
Straw, S. (2021) [98]	UK	05.03.2020 – 07.05.2020	R/C	CFS	R	> 18	PCR	485	159	71.2	16.9	259 (45.8)	frailty diff. for in-hospital mortality
Tehrani, S. (2021) [99]	Sweden	05.03.2020 – 28.04.2020	R/C	CFS	R	n/r	PCR	255	70	66	17	150 (59)	in-hospital mortality, ventilation
Thiam, C. N. et al. (2021) [100]	Malaysia	25.02.2020 - 27.05.2020	R/C	CFS	R	>60y	Clin	26	6	76,2	8,2	11 (42.3)	in-hospital mortality
van Steenkiste, J. et al. (2021) [101]	Netherland	09.03.2020 - 01.05.2020	R/C	CFS	R	>18y	n/r	32	24	79	74,5-83	22 (69)	frailty diff. for in-hospital mort
Verholt, A. B. et al. (2021) [102]	Denmark	01.03.2020 - 31.05.2020	R/C	MPI	R	>75y	Clin	100	37	82	77-84	44 (44)	in-hospital mortality; 30-day and 90-day mortality

S T U D Y	Origin	Recruitment period	Study type	Frailty Scale	Frailty assessment	Inclusion criteria		No. Of Patients		Age (years)		Sex	Outcomes
						Age (years)	COVID-19 diagnosis	Total	Deceased	mean / median	SD / IQ1-3	Male n (%)	
Welch, C. et al. (2021) [103]	Egypt, Spain, UK, Greece Ireland, Iraq, Italy, Libya, Saudi Arabia, Sudan, Turkey, USA	n/r	P/C+R/C	CFS	R/P	>18y	PCR or Clin	5711	1596	74	58-83	3149 (55.1)	in-hospital mortality
Wolfisberg, S. et al. (2021) [104]	Switzerland	26.02.2020 – 30.04.2020 and 01.10.2020 - 31.12.2020	R/C	CFS	R/P	>18y	PCR or Clin + rAT	486	92	65,9	14,7	317 (65.2)	in-hospital mortality; frailty diff. for in-hospital mort.; ICU admission

Table 1: Characteristics of included studies

Highlighted studies are included in the quantitative analyses. Age is reported using mean ± SD, or median (IQ 1–3) except: Davis P.R. where data was reported as mean (range). The method of frailty assessment was indicated by P for prospective and R in case of retrospective assessment. In case of prospective frailty assessment, if information about the training of the assessor was disclosed, it is marked by '+'

Abbreviations:

n/a not available, n/r no restriction, P/C prospective cohort, R/C retrospective cohort, CFS Clinical Frailty Scale, HFRS Hospital Frailty Risk Score, FiND Frail Non-Disabled questionnaire, PCR polymerase chain reaction, Clin diagnosis based on clinical suspicion, Rad radiologically suspected diagnosis, CT computer tomography based diagnosis, CXR chest X-rax, rAT rapid antigen test, SD standard deviation, IQ interquartile, OR odds ratio, ICU intensive care unit, LOH length of hospitalization, UK United Kingdom

Quantitative synthesis was performed for studies presenting data on mortality in patients living with frailty (CFS 4–9) compared to patients living without frailty (CFS 1–3) (*Fig. 3*). Sixteen studies were included in this analysis. Patients with CFS 4–9 had a significantly higher chance of mortality both in the UK subgroup (OR: 3.48; CI 2.74–4.42) and in the non-UK subgroup (OR: 2.98; CI 2.31–3.83) as compared to fit patients (CFS 1–3). In overall patients with CFS 4–9 had significantly, 3.12 times, higher odds for mortality (CI 2.56–3.81) than patients without frailty.

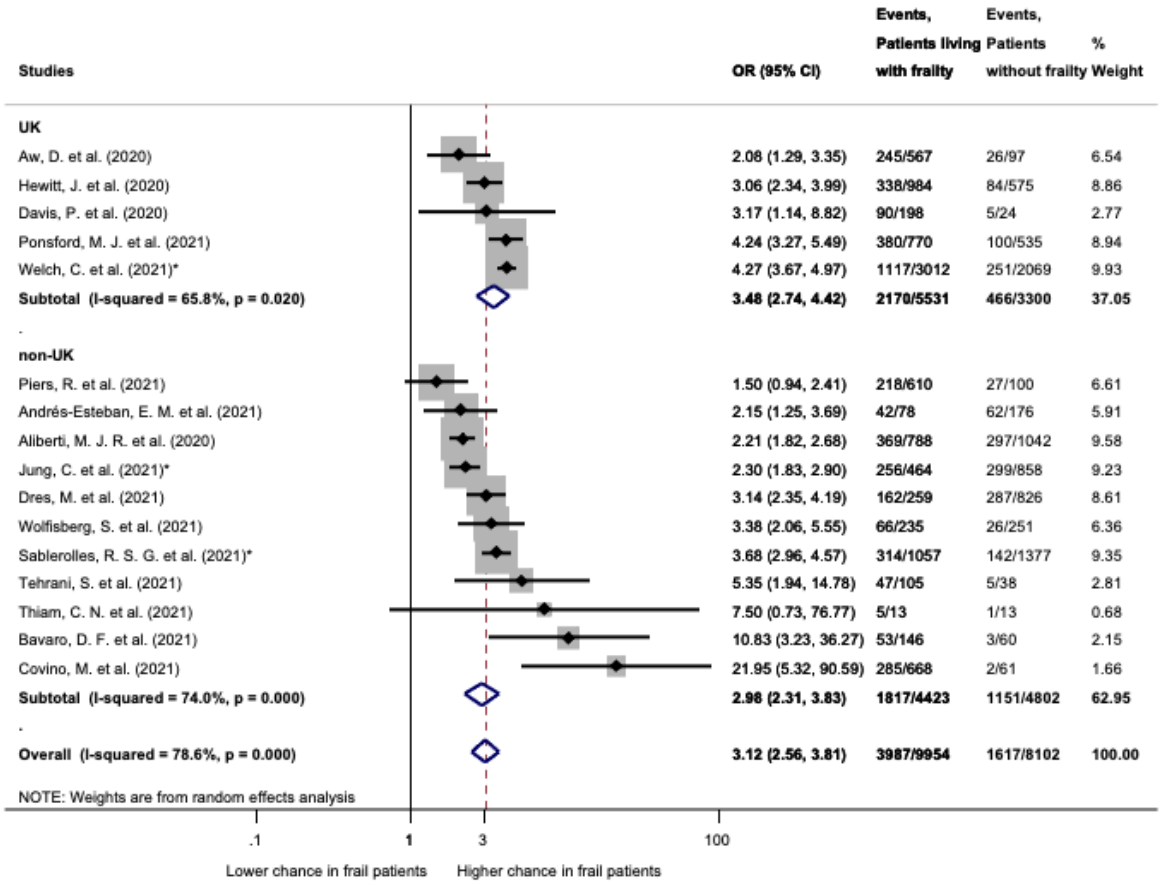

Figure 3: Mortality in patients with frailty (CFS 4–9) compared to not frail (CFS 1–3)
*Patients living with frailty (CFS 4–9) had significantly higher chance of mortality in both groups (UK and non-UK) and overall. Note that heterogeneity was significant in all cases. OR: odds ratio; CI: confidence interval. $p < 0.1$ was considered significant. *Indicates multicentric studies including patients from both groups, but the majority of patients affiliate to the correspondent subgroup*

In the analysis regrouped by age restriction at inclusion (Additional file 1: Fig. S8, online supplementary material; see chapter VII.1.2.7) studies including solely patients 65 years or older demonstrated significant odds for mortality (OR: 3.09; CI 2.08–4.60), as well as studies

without age restriction (OR: 3.27; CI 2.56–3.81) (CFS 4–9 vs 1–3). The regrouped analysis separating studies reporting in-hospital and 30-day mortality (Additional file 1: Fig. S7, online supplementary material; see chapter VII.1.2.7) showed significant results in both groups: OR: 3.39 (CI 2.70–4.26) and OR: 2.46 (CI 2.07–2.93) for in-hospital and 30-day mortality, respectively. However, assessing 30-day mortality demonstrated increasing statistical homogeneity (I^2 = 31.5%, p= 0.223) as compared to in-hospital mortality (I^2 = 72.6%, p = 0.000). No influential study was identified by the leave-one-out sensitivity analysis (Additional file 1: Fig. S9, online supplementary material; see chapter VII.1.2.7).

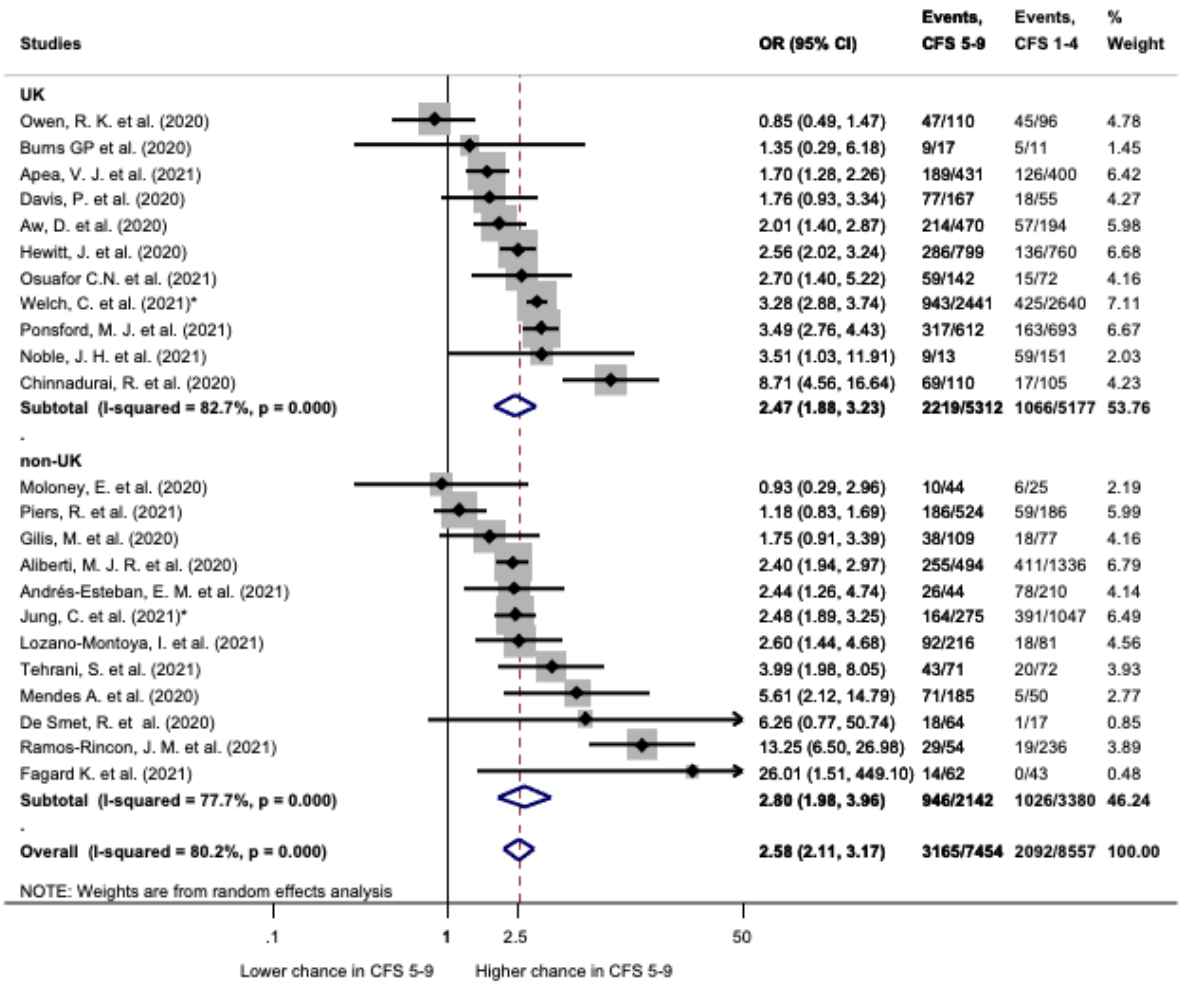

Figure 4: Mortality in patients with CFS 5–9 compared to CFS 1–4. *Patients with CFS 5–9 have significantly higher odds of mortality (OR: 2.58; CI 2.11–3.17). Patients from the UK (OR: 2.47; CI 1.88–3.23) and non-UK (OR: 2.80; CI 1.98–3.96) had significantly higher odds as well. Note that heterogeneity was significant in all cases. OR: odds ratio; CI: confidence interval. p < 0.1 was considered significant. *Indicate multicentric studies including patients from both groups, but the majority of patients affiliate to the correspondent subgroup*

In order to get a more thorough picture, studies comparing CFS 1–4 with CFS 5–9 were also quantitatively analysed (*Fig. 4*). This is in line with the original classification of the CFS, where a score greater than 4 indicated frailty [27]. Twenty-three studies presented sufficient data for this analysis. Frailty represented as CFS 5–9 demonstrated still significantly higher odds ratio for mortality: 2.58 (CI 2.11–3.17) as compared to CFS 1–4 (*Fig. 4*). Patients from the UK and from other countries had comparable odds ratios 2.47 (CI 1.88–3.23) and 2.58 (CI 2.11–3.17), respectively (*Fig. 4*). Analysing subgroups with and without age restriction (Additional file 1: Fig. S12, online supplementary material; see chapter VII.1.2.7), and 30-day and in-hospital mortality (Additional file 1: Fig. S11, online supplementary material; see chapter VII.1.2.7) could not achieve homogenization of results. All assessed subgroups showed significant heterogeneity, but an influential study could not be identified by the leave-one-out sensitivity analysis (Additional file 1: Fig. S13, online supplementary material; see chapter VII.1.2.7). Patients with CFS 1–5 and CFS 6–9 were also compared (Additional file 1: Figs. S15–S17, online supplementary material; see chapter VII.1.2.7). The overall odds ratio for mortality was 2.55 (CI 2.13–3.07). Again, all subgroups demonstrated significant results, but heterogeneity was significant in all cases, although no influential study was identified by the leave-one-out sensitivity analysis (Additional file 1: Fig. S18, online supplementary material; see chapter VII.1.2.7).

Similarly to our results, multiple logistic regression adjusted for age, sex, respiratory rate, FiO_2, consolidation, and urea resulted in an OR of 2.55 (CI 1.74–3.74) for 30-day mortality and OR: 2.60 (CI 1.34–5.06) for 72-h mortality by Bradley et al. for patients with CFS ≥ 5 [105].

Maguire et al. reported on a retrospective cohort of 261 patients. Unfortunately, the presented data was contradictory, thus could not be included in the quantitative synthesis [106].

Nineteen studies reported the mean or median frailty in survivors and non-survivors, of which 12 were included in quantitative synthesis (Additional file 1: Fig. S21, online supplementary material; see chapter VII.1.2.7). Non-survivors generally scored significantly higher using the CFS than survivors (overall WMD: 1.21; CI 0.83–1.59). Differences were significant for in-hospital and 30-day mortality separately. Regrouping by country also yielded significant results in both subgroups (Additional file 1: Fig. S20, online supplementary material; see chapter VII.1.2.7). No influential study was identified by the leave-one-out sensitivity analysis (Additional file 1: Fig. S22, online supplementary material; see chapter VII.1.2.7).

Similarly to the results of the quantitative synthesis, Brill et al. reported, that the median CFS was 4 in discharged patients versus 5 in patients who died ($p = 0.014$) [60].

Cecchini et al. reported on a hospital cohort of 122 geriatric patients [107]. Median CFS was significantly higher in non-survivors than survivors (7 vs 6, respectively; p = 0.001). IQR was not appropriately stated, thus could not be included in the analysis. Cuvelier et al. included 20 severe COVID-19 patients admitted to a geriatric intermediate care unit, who were not eligible for any higher level treatment [108]. Non-survivors had higher median CFS (6.0, IQR: 5.5–6.5) compared to survivors (4.5, IQR: 3.5–6.0). In both groups two patients had missing CFS data. Fallon et al. reported on a hospital cohort of 86 elderly patients [109]. Non-survivors had a mean CFS of 5.2 compared to survivors' 4.1 (SD was not published). Hoek et al. provided data on solid organ transplant recipients. The mean CFS was 5.8 points for patients who died, while 1.92 points for survivors (SD was not disclosed) [74]. Koduri et al. reported on a single center cohort of 500 patients [110]. Non-survivors had significantly higher median CFS score (5, min: 1, max: 9) than survivors (3, min: 1, max: 9), ($p < 0.001$).

McWilliams et al. only included COVID-19 patients admitted to the ICU, therefore could not be pooled. ICU mortality and hospital discharge destination were detailed by CFS score categories [111]. 67 patients died in the ICU, who's CFS score was significantly higher than ICU survivors' ($p < 0.001$). Only one patient died in the hospital after ICU discharge, who's CFS score is not detailed.

Van Steenkiste et al. included 32 severe patients, who were not deemed eligible for invasive mechanical ventilation and received high-flow nasal oxygen therapy as a rescue [112]. There was no difference in median CFS score between survivors and non-survivors (4, IQR: 4–6 vs 4, IQR: 4–6, p = 0.44).

Frailty measured by the Hospital Frailty Risk Score

We performed a quantitative synthesis of three studies reporting mortality in patients living with frailty using Hospital Frailty Risk Score (*Fig. 5*). Two of these studies analysed nationwide recorded electronic databases (Navaratnam et al. from England and Kundi et al. from Turkey), including over 75,000 patients. The third study was a hospital cohort study from Spain (Ramos-Rincon et al.). Compared to the low-risk group (HFRS < 5), patients with intermediate and high risk of frailty had a significantly higher chance for mortality (OR: 1.98; CI 1.89–2.07). Results were statistically homogenous ($I^2 = 0.0\%$; p = 0.583).

Apea et al. reported HFRS in a cohort from five acute hospitals in London. Since there is a high potential for an overlapping patient population with Navaratnam et al., Apea et al. have been excluded from this analysis. Based on their data calculated odds ratio for mortality was

5.21 (CI 4.03–6.74) in the intermediate and high-risk group (HFRS ≥ 5) compared to the low-risk group (HFRS < 5).

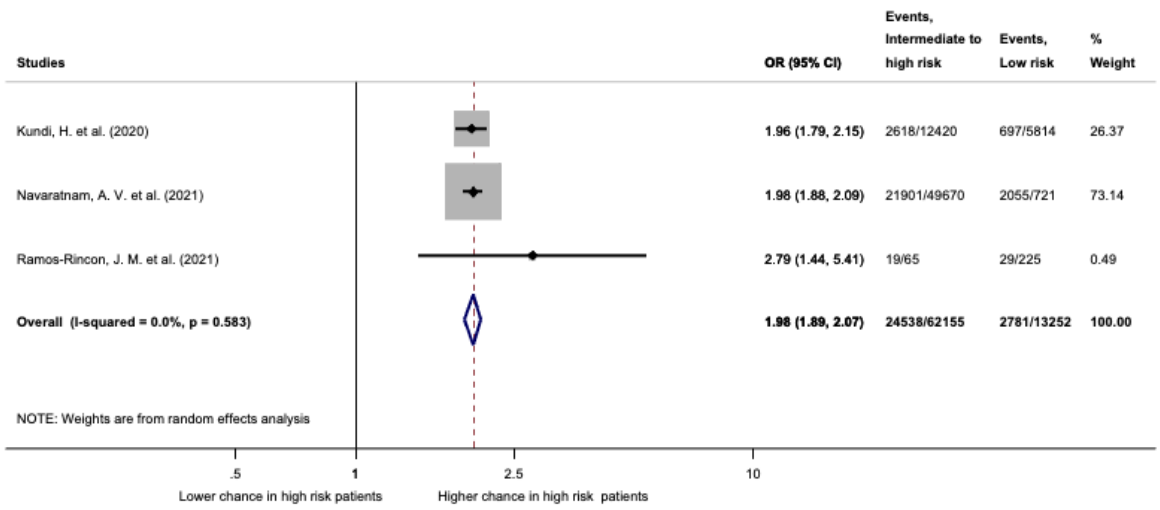

Figure 5: Mortality assessed by the Hospital Frailty Risk Score. *Patients with intermediate and high risk (HFRS ≥ 5) have significantly higher odds of mortality (OR: 1.98; CI 1.89–2.07) compared to patients with low risk of frailty (HFRS < 5). This analysis was statistically homogeneous (I^2 = 0.0%, p = 0.583). OR: odds ratio; CI: confidence interval. p < 0.1 was considered significant*

Frailty measured by the Multidimensional Prognostic Index

A quantitative synthesis of three studies reporting on mortality associated with frailty measured by the MPI was undertaken (Additional file 1: Fig. S24, online supplementary material; see chapter VII.1.2.7). Contradictorily, in the study by Maki et al., mortality in patients with frailty (MPI 2 and 3) was 16.7% as compared to 33.3% in patients without frailty (MPI 1) [82]. This could be due to the very low sample size (n = 18). The overall odds ratio for mortality in MPI 2 + 3 compared to MPI 1 was 4.31 (CI 0.91–20.49) but did not reach statistical significance. Although all studies reported in-hospital mortality, there was significant, substantial heterogeneity (I^2 = 68.8%, p = 0.041).

Verholt et al. also reported a significantly higher chance of 30-day and 90-day mortality in patients living with frailty (MPI 2 + 3) in contrast to patients with MPI 1 [113].

Frailty measured by miscellaneous tools

Two studies presented data on mortality in association with a modified frailty index (mFI) [114, 115]. Fumagalli et al. included 221 patients aged 75 or older from two centres, [114].

44.3% of deceased patients were frail, in contrast to 29% of survivors. The absence of frailty was significantly associated with survival (adjusted HR 0.6; CI 0.39–0.94; p = 0.024). Kurtz et al. presented data on 13,301 patients. Frailty indicated by mFI was associated with worse 30-day and 60-day survival. (MFI > 2 60-day mortality HR: 1.38; CI 1.15–1.64; p < 0.001) [115].

Steinmeyer et al. reported on a geriatric cohort of patients, where frailty was assessed with the Frail Non-Disabled Survey (FIND). According to their analysis frailty was not correlated with mortality [97].

VII.1.3.4. ICU admission

Ten studies reported on the association of frailty indicated by the CFS and ICU admission. We conducted two analyses with different partitions of CFS (1–3 vs 4–9 and 1–4 vs 5–9). Due to the arbitrary grouping of the CFS by different authors, 7 and 6 studies could be included in the analyses of CFS 1–3 vs 4–9 and CFS 1–4 vs 5–9, respectively.

The analysis of CFS 1–3 vs. 4–9 resulted in an overall odds ratio of 0.28 (CI 0.12–0.64), although displaying considerable statistical heterogeneity (I^2 = 95.1%, p = 0.000). In order to clarify possible reasons behind this, we divided the pool into two distinct subgroups. This resulted in statistical homogeneity in both groups (I^2 = 0.0%, p = 0.732 and I^2 = 35.2%, p = 0.214) (*Fig. 6*). One possible explanation might be that studies included in the first group originated from countries where CFS was included in guidelines for advance care planning (Belgium, the Netherlands, the UK). Here, frailty resulted in a significantly lower chance of ICU admission (OR: 0.13; CI 0.09–0.17). In contrast, frailty-based advance care planning was not applied in the majority of centres included in the second group. It is to note that Sablerolles et al. is a European multicentric retrospective cohort study in which centres from Belgium, the Netherlands, France, and the UK recruited patients as well, but more than 50% of the included patients originated from other European countries. In this group, frailty did not significantly reduce the chance for ICU admission (OR: 0.83; CI 0.63–1.09) (*Fig. 6*). The leave-one-out sensitivity analysis did not identify any influential study (Additional file 1: Fig. S25, online supplementary material; see chapter VII.1.2.7).

In another quantitative analysis of studies, we examined association of ICU admission in a patient group with further advanced frailty (CFS 5–9) compared to robust and very mildly frail patients (CFS 1–4). In the quantitative synthesis, 6 studies could be included (Additional file 1: Fig. S27, online supplementary material; see chapter VII.1.2.7). Overall, advanced frailty (CFS 5–9) resulted in a significantly lower chance of ICU admission (OR: 0.09; CI 0.04–0.22).

Although a subgroup analysis was not applicable, an analogical tendency can be observed, as in *Fig. 6*, resulting in significant overall heterogeneity (I^2 = 64.9%, p = 0.014). The leave-one-out sensitivity analysis did not identify any influential study (Additional file 1: Fig. S28, online supplementary material; see chapter VII.1.2.7).

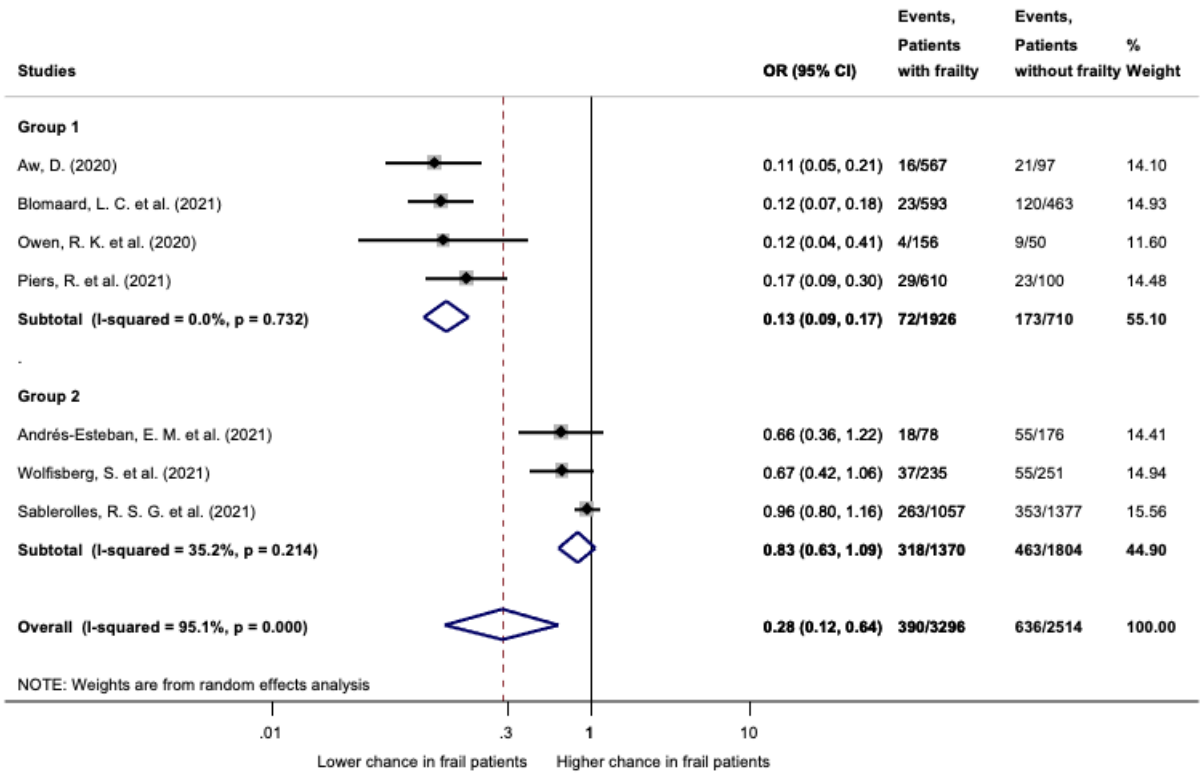

Figure 6: ICU admission in patients with frailty indicated by CFS 1–3 vs 4–9. *Patients living with frailty (CFS 4–9) have significantly lower odds to be admitted to the ICU (overall OR: 0.28; CI 0.12–0.64). In group 1 chance for ICU admission was significantly lower in patients with frailty (OR: 0.13; CI 0.09–0.17), however in group 2 to there was no significant difference (OR: 0.83; CI 0.63–1.09). For further explanation please see text. Please note, that in contrast to the significant overall heterogeneity, both subgroups were statistically homogeneous. OR: odds ratio; CI: confidence interval. p < 0.1 was considered significant*

VII.1.3.5. Length of stay

The average length of stay was reported in seven studies. Five studies reported on CFS, one study on HFRS and one on both. Arbitrary categorization and different statistical methods of data presentation made quantitative analyses unfeasible. A brief summary of results can be found in Additional file 1: P. 34, online supplementary material; see chapter VII.1.2.7) The

observed outcomes show substantial heterogeneity and no meaningful, generalizable conclusion can be drawn.

VII.1.3.6. Publication bias

Eggers's test was only conducted where at least 10 studies were included in the analysis. Visual examination of funnel plots and Eggers' tests did not show small-study effect for any examined outcomes, but one. (Additional file 1: Figs. S10, S14, S19, S23, S24, S26, S29, online supplementary material; see chapter VII.1.2.7). On the funnel plot of ICU admission CFS 1–3 vs 4–9 (Additional file 1: Fig. S10, online supplementary material; see chapter VII.1.2.7) strong asymmetry can be observed, which may be due to publication bias. HFRS and MPI could not be examined due to the low number of studies included in the analyses.

VII.1.4. Discussion

In this systematic review and meta-analysis of the relationship between frailty and mortality, ICU admission, and LOH in COVID-19 patients, which included 54 studies and 152,628 subjects, we found that frailty was associated with significantly elevated odds for mortality, and frail patients were less likely to be admitted to the ICU.

Despite advances in critical care management, mortality of severe respiratory failure, especially with COVID-19, remains high [116, 117]. Advanced organ support—the cornerstone of intensive care—may interfere with human dignity. The relatively high mortality and the required work intensity mean a burden for the patient, relatives, and staff alike and are—last but not least—costly [118, 119]. Therefore, prolonged, advanced organ support might be regarded as medically futile in those cases whose chances are extremely limited for survival [120, 121]. Hence, predictors of survival have been extensively researched. Due to the unprecedented load on ICUs during the pandemic of COVID-19, implementing a reliable tool to identify those who could not benefit from intensive care would be of utmost help for clinicians, patients, and relatives alike.

It is well known that age on its own can be misleading in outcome prediction [122]. A potential alternative is the assessment of frailty, a concept that has already been supported during the COVID-19 pandemic by some studies and recent meta-analyses [35-42]. However, multiple methodological flaws were detected in previous meta-analyses, such as pooling of odds, risk and hazard ratios, as well as pooling of different frailty tools together [35, 41]. In

terms of CFS we disagree with the calculation of dose response, while single CFS increments cannot be compared [36]. Furthermore, Kastora et al. demonstrated a variable increase in mortality between single CFS increments [39]. In most of those studies reporting on CFS, categorization was arbitrary and the authors did not report outcomes for each CFS score except five included studies [73, 123-126]. In contrast to recent meta-analyses, we sought to analyse the most meaningful arrangements of CFS groups dividing patients into a fit to minimal degree of frailty group compared to patients with more advanced level of frailty. Consequently, we only included studies into each analysis, which reported data on the respective grouping.

It is important to note, that frailty assessment-based decision-making has not been implemented worldwide. According to our literature search (up to September 2021), several countries (UK, the Netherlands, Belgium, and France), with well resourced, high-quality health care advised the use of CFS in decision-making in their COVID-19 guidelines; in contrast to Central and Eastern Europe [127-129].

Limitation of treatment, i.e.: denying advanced levels of care to patients based on the level of frailty might increase mortality, in a way of a self-fulfilling prophecy. As a remarkable portion of the studies included in our meta-analysis originated from countries where frailty-based ceiling of care decision-making protocols are already implemented, this fact on its own can influence the observed mortality and therefore our results as well. However, there is an increasing body of evidence from other countries where frailty-based treatment limitations are not included in daily routine patient management. Kundi et al. reports in a Turkish nation-wide assessment that high-risk frail patients (Hospital Frailty Risk Score > 15) had higher odds for all-cause mortality (adjusted OR: 2.084; CI 1.799–2.413) but also a higher chance for ICU admission (adjusted OR: 2.221; CI 1.951–2.527), as well as receiving invasive mechanical ventilation (adjusted OR: 1.769; CI 1.531–2.046) [78]. In a large European multicentric retrospective study Sablerolles and colleagues provided evidence that compared to fit patients (CFS 1–3), patients with frailty (CFS 6–9) had a significantly higher chance of ICU admission (adjusted OR: 1.54; CI 1.21–1.97), and in addition, those admitted to the ICU were significantly more likely to die (OR: 1.81; CI 1.14–2.87) [96]. These findings align with our results, suggesting that although there might be some effect of limiting higher level of care, the observed high mortality rate in frail COVID-19 patients cannot merely be explained by that. Furthermore, our results also suggest that measuring frailty could potentially help in the selection process of those patients who could not benefit from intensive care.

As the clinically more aggressive variants are spreading across the world, including Eastern and Central Europe—the home region of the authors—the effective allocation of resources

would be of utmost importance. These countries were more-or-less spared during the first wave and also in the second wave when mortality rates were higher in Western and Northern European countries [130-132]. However, the third wave proved devastating in this region of Europe from both the ICU-burden and the survival perspectives [5].

Although ethical concerns were raised against frailty-based decision-making, this method potentially provides a professional and transparent scaffold for health care providers [133, 134]. It has also been shown that the decision to withhold or withdraw life-sustaining treatment from patients older than 80 years in the ICU correlates with income and religious influence. In countries with lower income and higher religiosity, high-intensity critical care treatments are less frequently withdrawn, and the decision does not depend on age and ICU bed availability [135]. In a recent multicentre, multinational prospective observational study on 1346 older adult (> 70) ICU COVID-19 patients, frailty provided relevant prognostic information in addition to age and comorbidities [124]. Furthermore, an indirect comparison by Kow et al. has indicated that frail individuals may be overrepresented among the COVID-19 patient population and given a rather strong hint that the presence of frailty may lead to a higher risk of acquisition of COVID-19 [136]. In addition to frailty, severity of the acute illness also has a major role in clinical outcomes, especially in the elderly, more frail population. It is also important to note that patient care pathways could also have an impact on the final outcome, however, detailed discussion of this issue is beyond the scope of the current manuscript.

Finally, it should be mentioned that frailty must never be applied as a stand-alone cutoff value in patient management. However, it should be part of a patient based, individualized decision making. Therefore, it would be desirable that based on the available scientific evidence, health authorities encouraged and supported the implementation of frailty-based risk assessment into national guidelines.

VII.1.4.1. Strengths and limitations

To our knowledge, this is the most detailed and comprehensive, up to date evaluation of frailty in COVID-19, separately analysing 30-day and in-hospital mortality, studies from and outside of the UK and reporting on different age groups, as well as including five different frailty assessment scores. We also assessed the relationship between frailty and ICU admission. In contrast to other meta-analyses, we only pooled together studies using the same frailty score, same frailty range, and similar statistical tools. Another methodological strength is that leave-one-out sensitivity analysis was also performed to identify influential studies. The majority of

the included studies were retrospective and carried high risk of bias, therefore could introduce bias in our analysis. Nevertheless, one of the most important limitations of our study is the considerable heterogeneity that was a common feature in many of the analyses. The explanation could lie in standard medical practice, age distribution, and nurse-to-patient ratio, which can differ between countries and hospitals. Another limitation is that we did not have access to individual patient data. Furthermore, studies implementing frailty assessment in COVID-19 were not published from Central and Eastern European countries; therefore, they were not represented in the quantitative analyses.

VII.1.5. Conclusion

To the best of our knowledge, this is the largest, most recent and comprehensive meta-analysis of studies in this topic today in COVID-19 patients. Our results show that frailty as determined by CFS is strongly associated with in-hospital and 30-day mortality and may also play an important role in determining eligibility for ICU admission in patients suffering from COVID-19. These findings have some implications for research: further evaluation of the effects of frailty-based patient management on ICU admission, ICU mortality as well as long term outcomes should also be investigated in the future within the scope of high-quality, low risk of bias studies. Regarding implications for practice, we believe that frailty-based patient management should be included in international COVID-19 treatment guidelines.

VII.2. Investigating the association between IL-6 antagonist therapy and blood coagulation in critically ill patients with COVID-19: a protocol for a prospective, observational, multicentre study

VII.2.1. Introduction

The emerging SARS-CoV-2 virus has shed new light on the crosstalk between the immune and the blood coagulation system. From the pathophysiological standpoint in COVID-19 infection, the thromboinflammatory process is initiated by the host's exaggerated systemic inflammatory response, also called 'dysregulated immune response' that activates both the inflammatory and the coagulation cascade directly by inflammatory mediators and indirectly by causing endothelial cell injury [22]. These mechanisms altogether contribute to the imbalance of the haemostasis that is characterised by a procoagulant state that is characterised by increased number of thrombotic complications even despite the implementation of thromboprophylaxis [23]. Current guidelines seem to agree that the resulting procoagulant state cannot be reduced by higher intensity anticoagulation neither without counteracting its benefits by the increased risk of bleeding in case of critically ill patients [25, 137].

This COVID-19 associated imbalance in the procoagulant and anticoagulant factors is the effect of the cytokine storm caused by inflammation and endothelial cell injury. One of the proinflammatory cytokines that have a key role in the crosstalk between the immune system and blood coagulation is the interleukin-6 (IL-6). It is a pleiotropic cytokine that has a role in haematopoiesis, inflammatory processes and oncogenesis [138]. Regarding the effects on blood coagulation, animal studies have pointed out that the elevation of IL-6 alters the balance of this system by inducing thrombocytosis, platelet hyperactivity and aggregation [139].

In an experimental study on healthy volunteers, IL-6—among other cytokines—was added to the blood and the changes caused by the cytokine in the blood coagulation were evaluated by using viscoelastic haemostasis assay (VHA) [140]. As the effect of IL-6 administration, a fragile, unstable clot was formed quicker than in the healthy volunteers' blood prior to the addition of the cytokine. Furthermore, a proteomic study showed that very high levels of IL-6 can increase the level of SERPIN and CPB2/TAF carboxypeptidases that have an inhibitory effect on fibrinolysis [141].

IL-6 antagonists were introduced in the guidelines of COVID-19 treatment in case of severely ill patients with increased need for oxygen support, like high-flow nasal oxygen therapy, non-invasive or invasive mechanical ventilation [142]. According to the current literature, few studies have evaluated the changes that this therapy caused in the immune

response and the crosstalk between the blood coagulation system by using viscoelastic haemostatic assays in patients with COVID-19. Therefore, this study could provide further data on this topic.

VII.2.2. Objectives

We aim to evaluate whether the immunomodulation with an IL-6 antagonist is associated with an improved haemostasis in patients with COVID-19 as measured by viscoelastic tests. Our main objectives are the following:

- To assess the changes of the coagulation profile and the fibrinolytic system by VHA parameters before and after immunomodulation with IL-6 antagonist administration.

- To test the associations between coagulation, endothelial damage and inflammatory parameters before and after IL-6 antagonist therapy.

VII.2.3. Methods and Analysis

VII.2.3.1. Study design and setting

Participating sites	Progressivity level	Number of beds
Department of Anaesthesiology and Intensive Care Szent György Hospital Fejér County (district general hospital)	III	31
Department of Anaesthesiology and Intensive Care Flór Ferenc Hospital of Pest County (district general hospital)	III	10
Department of Anaesthesiology and Intensive Care Semmelweis University (university hospital)	III	41
Department of Anaesthesiology and Intensive Care University of Pécs (university hospital)	III	25

Table 2: Type and main characteristics of the ICUs
Progressivity level is measured from I to III, where III is the institution with most facility and personal thus can take care of a wide variety of pathology and I are institution with reduced personnel and facilities. ICU, intensive care unit.

This is a prospective, multi-centre observational study of critically ill patients with COVID-19 admitted to the intensive care unit (ICU). Currently, there are four multi-disciplinary ICUs in Hungary that will enrol patients in the study between January 2022 and December 2023. Details and main characteristics of the ICUs are summarised in *Table 2*. Nevertheless, the study is open for other sites willing to participate. This study was designed in accordance with the amended Declaration of Helsinki and the original study protocol's ethical approval was given by the Medical Research Council of Hungary (1405-3/2022/EÜG). The trial is registered on ClinicalTrials.gov.

VII.2.3.2. Patient population

Inclusion and exclusion criteria are summarised in *Table 3*. There will be no recruitment of patients as they will be selected based on the decision of the treating physician from the patients admitted to the ICU.

Inclusion criteria	**Exclusion criteris**
1. Adults (>18 years old)	1. The patient had previously been administered one of the following immunomodulating drugs: anakinra, tocilizumab, sarilumab
2. Clinical diagnosis of SARS-CoV-2 infection with rtPCR confirmation	2. Presence of any condition or drug in the medical history that can lead to immunosuppression
3. Disease severity that has the indication of immunomodulation therapy with interleukin-6 antagonist: acute respiratory failure that requires invasive, non-invasive ventilation, non-invasive O_2 therapy or high-flow nasal oxygen therapy with the following parameters: FiO_2 > 0.4, flow > 30 L/min and CRP >75 mg/L	3. Suspicion of infection (active tuberculosis, bacterial, viral, fungal) or level of procalcitonin higher than 0,5 ng/mL at the enrolment of the patient
	4. The number of thrombocytes lower than 50×10^9/L
	5. More than >120 hours passed between the admission to the ICU and the administration of an interleukin-6 antagonist
	6 Administration of any of the following drugs the week before or during the study: fibrinolytic therapy, factor products (PCC, ATIII, FVIIa, FXIII), fibrinogen, desmopressin, tranexamic acid, blood products (fresh frozen plasma, thrombocyte concentrate)
	7. Pregnancy
	8. The patient or his legal guardian does not sign the consent

Table 3: Eligibility criteria.
ATIII, antithrombin III concentrate; CRP, C reactive protein; FiO2: fraction of inspired oxygen; FVIIa, factor VIIa concentrate; FXIII, factor XII concentrate; PCC, prothrombin complex concentrate; rtPCR, reverse transcription PCR.

VII.2.3.3. Data collection

The patients' data will be collected prospectively. Data on age, sex, comorbidities, height, weight, body mass index, lifestyle, frailty using the Clinical Frailty Scale [27, 28] and current status will be recorded. Clinical and laboratory parameters, such as blood pressure (systolic, diastolic), heart rate, peripheral capillary oxygen saturation (SpO_2), respiratory rate, body temperature, disease severity scores, ventilation parameters, blood gas parameters, VHA results will be recorded at set time intervals (see later). All the medication that the patient has taken during the study period will be noted. Blood culture samples will also be taken when indicated to exclude superinfection thus ensuring that these will not influence the results of the study.

Data entry of the variables of interest will be performed by the investigators at the participating sites using a web-based database. All participating sites will use the same electronic case report forms. The patients will receive a unique identifier to anonymise their data.

VII.2.3.4. Laboratory data and VHA

Blood samples necessary for laboratory analysis and VHAs will be obtained at the same time, on the day of inclusion (T_0) and then 24 hours (T_1), 48 hours (T2) 5 days (T_3) and 7 days (T_4) later. *Table 4* shows the measurement points of the specific inflammatory and coagulation parameters relative to the administration of IL-6 antagonist.

For VHA, the ClotPro® device (Haemonetics Corporation, Boston) will be used. Blood will be collected in tubes prefilled with sodium citrate 3.2%. To obtain information about the coagulation in vivo the EX-test ($CaCl_2$ recalcifies the sample and recombinant tissue factor activates coagulation), FIB-test (detection of functional fibrinogen by recombinant tissue factor and dual platelet inhibition), IN-test (intrinsic screening test activated by ellagic acid, sensitive to heparin and coagulation factors), TPA-test (activation of fibrinolysis by recombinant tissue plasminogen activator) and RVV-test (direct activation of FXa) and ECA-test (direct activation of thrombin) will be used. CT (clotting time), CFT (clot formation time), ∝-Angle, MCF (maximum clot firmness), ML (maximum lysis) will be recorded for EX-test, FIB-test, IN-test, RVV-test. LT (lysis time), LOT (lysis onset time), ML, CLI-30, CLI-45 (clot lysis index at 30 and 45 min, respectively) will be recorded for TPA-test. LOT, CLI-30, CLI-45 will be recorded for the EX-test as well.

Day / hours	Time point	Conventional laboratory parameters (local laboratory)	ClotPro® tests	Blood sample (central laboratory)
Day 0	T_0	wbc., infl., biochem., coag.	EX, IN, FIB, TPA, RVV, ECA	plasma, serum
ADMINISTRATION OF IL-6 ANTAGONIST				
+ 24 hours	T_1	wbc., infl., biochem., coag.	EX, IN, FIB, TPA, RVV, ECA	
+ 48 hours	T_2	wbc., infl., biochem., coag.	EX, IN, FIB, TPA, RVV, ECA	plasma, serum
5. day	T_3	wbc., infl., biochem., coag.	EX, IN, FIB, TPA, RVV, ECA	
7. day	T_4	wbc., infl., biochem., coag.	EX, IN, FIB, TPA, RVV, ECA	plasma, serum

Table 4: Timeline of the assessment of inflammatory and coagulation parameters relative to the administration of IL-6.
ECA-test, ecarin clotting assay test; EX-test, extrinsic coagulation pathway test; FIB-test, functional fibrinogen test; IN-test, intrinsic coagulation pathway test; RVV-test, Russell's viper venom reagent test; TPA-test, tissue plasminogen activator test; wbc., whole blood count; infl., inflammatory parameters; biochem., clinical biochemistry; coag., conventional coagulation parameters

The results of the routine laboratory tests such as the whole blood count, inflammatory parameters (procalcitonin, C reactive protein, ferritin), clinical biochemistry (creatine, blood urea nitrogen (BUN), serum glutamic oxaloacetic transaminase (GOT), serum glutamic pyruvic transaminase (GPT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), serum bilirubin, direct bilirubin, creatine kinase (CK), lactate dehydrogenase (LDH) and conventional coagulation parameters (international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, D-dimers) will be collected every day.

Blood sample will be drawn for further analysis (in central laboratory) in a native tube, without anticoagulants or preservatives to measure the level of IL-6 and syndecan-1 from serum and another tube prefilled with sodium citrate 3.2% for the laboratory parameters of fibrinolysis from plasma (plasminogen, plasminogen activator inhibitor/PAI-1, von Willebrand factor antigen and activity, and factor VIII) that will be measured on the day of admission and then 48 hours and 7 days later. These samples will be centrifuged and will be stored at –80°C. All collected samples will be analysed in the same laboratory.

VII.2.3.5. Outcomes

The *primary outcome* is the change of the fibrinolytic system measured by the LT and LOT before (T_0) and after immunomodulation therapy (T_2). As our time points of measurements are 24 hours, 48 hours, 5 days and 7 days after the administration of IL-6 antagonist and the effect of it are relatively shortly seen in inflammatory parameters after administration, we decided to use the parameters immediately before and 48 hours after the administration of the drug in our primary analysis.

In addition, the study will investigate the following *secondary outcomes*:

- Change of the fibrinolytic system assessed by VHA and measured by the plasminogen, PAI-1 before (T_0) and after immunomodulation therapy ($T_{1,2,3,4}$).
- Change in blood coagulation parameters that evaluate hypercoagulable state before (T_0) and after immunomodulation therapy ($T_{1,2,3,4}$) measured by Clotpro® device assays comparing: CT, CFT, MCF.
- Correlation between inflammatory and blood coagulation parameters. For the assessment of this endpoint, we will use the results of the inflammatory laboratory parameters as procalcitonin, C reactive protein, ferritin, LDH and the blood coagulation parameters measured by the ClotPro® (CT, CFT, ∝-Angle, MCF, ML, CLI-30, CLI-45, LT, LOT, ML).
- Correlation between biomarkers of endothelial injury and blood coagulation parameters. For the assessment of this endpoint, we will use the results of the biomarkers of the endothelial damage as syndecan-1, von Willebrand factor activity and antigen, Factor VIII and the blood coagulation parameters measured by the ClotPro®: CT, CFT, ∝-Angle, MCF, ML, CLI-30, CLI-45, LT, LOT, ML and plasminogen, PAI-1.

VII.2.3.6. Sample size and statistical analysis

Since there is insufficient data in the literature to perform pro forma sample size calculation, we decided to initially enrol 30 patients (based on Bachler et al. [143]), after which an interim analysis and final sample size calculation (power: 80%, type I error: 5%) for the primary endpoint (change in LT between T_0 and T_2) will be performed.

Analysis of data will be performed independently based on each specific aim using the R statistical software (R Core Team (2021); R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The collected data will be evaluated using descriptive statistical methods. Categorical variables will be expressed as frequencies (counts) and relative frequencies (percentages) and continuous data will be expressed as minimum, maximum, mean ± SD or median with IQR (Q3−Q1). In case of missing data, the participant's data will not be used for further analysis for the specific outcome where there is any missing data, but other data collected from the patient will be used for other outcomes.

We will use a mixed effect model to analyse the data where the random effect will be patient ID. To observe the correlation between the laboratory parameters, we will use Spearman's rank correlation analysis. Statistical significance defined as $p < 0.05$. The p values will be corrected by the false discovery rate method if necessary.

VII.2.3.7. Trial management

The trial will be coordinated from the Centre for Translational Medicine, Semmelweis University, including the chief investigator, selected co-investigators, project manager, trial statistician, clinical trial coordinator and IT staff, who will oversee the running of the trial and meet monthly.

VII.2.3.8. Patient and public involvement

There was no patient or public involvement in the design and planning of this observational study.

VII.2.3.9. Ethical considerations and dissemination

This study was designed in accordance with the amended Declaration of Helsinki. The Committee of Scientific and Research Ethics of the Medical Research Council of Hungary approved the study with the following registration number: 1405-3/2022/EÜG. As this is not an interventional study, participation in this study will not interfere with the treatment of the patient, hence safety issues are not concerned. The standard of care of the participating centres is defined by the Hungarian national guidelines on the treatment of severe COVID-19[144].

From all participants and/or legal representatives written, informed consent will be obtained before inclusion and the opportunity to ask questions will be offered.

All participants have the right to withdraw from the study at any point without giving any reason. We will present analysed data at domestic and international medical conferences and will publish them as scientific papers in peer-reviewed journals. Data will be reported in accordance with "Strengthening The Reporting of Observational Studies in Epidemiology" guidelines for observational studies [145].

VII.2.4. Discussion

Overwhelming inflammatory response is a frequent finding in critically ill patients with COVID-19 that potentially could be treated with immunomodulatory therapies such as IL-6 antagonists [146, 147]. Although inflammation and coagulation disorders in COVID-19 are well documented, but whether anti-IL-6 therapy has any effect on the haemostasis has not been thoroughly investigated yet.

The procoagulant state induced by COVID-19 infection was investigated in various studies. At first, it was described as a state that mimics disseminated intravascular coagulopathy [148]. Later Iba et al. proposed the following criteria [149]: (1) decrease in platelet count (<150×109 /L); (2) increase in D-dimer (more than two times the upper limit of normal); (3) >1 s prolonged prothrombin time or INR > 1.2; (4) presence of thrombosis and if the patient meets one of the above four criteria and also one or more of following criteria: (i) increase in fibrinogen level; (ii) increased von Willebrand factor (more than two times the upper normal limit); (iii) presence of lupus anticoagulant and/or high-titre antiphospholipid antibodies, they are defined as 'risk of COVID-19 associated coagulopathy'.

Besides conventional laboratory parameters, the coagulation disorder caused by COVID-19 was described using VHA tests as well. Bareille et al reviewed the available literature on COVID-19 associated coagulopathy and they found that all of the analysed studies reported a hypercoagulable state with increased clot strength often accompanied by impaired fibrinolysis [150]. VHAs, in general, have not only the potential advantage of point-of-care testing but studies have shown that they give a better insight into the dynamic changes of coagulation in vivo as the results of several studies have suggested lower mortality in the group of patients whose transfusion strategy was guided by VHA compared with conventional laboratory parameters [151].

The level of IL-6 correlates with the disease severity in patients with COVID-19 [152]. Therefore, the rationale of using IL-6 antagonist to decrease the severity of inflammatory response in COVID-19 has been postulated and later tested in clinical trials [21]. One of the available drugs on the market in Hungary is Tocilizumab, an anti-interleukin-6 receptor (IL-6R) recombinant monoclonal antibody. It is used primarily in rheumatic disorders, but it is efficient in the treatment of cytokine release syndrome, which can appear as a side effect of haematologic treatments [153]. The benefits of immunomodulation with Tocilizumab have been shown in critically ill patients with COVID-19 and this indication is included in WHO living guidelines [20, 21, 142, 154].

There have been various trials that investigated how to counteract the detrimental effects of the abovementioned dysregulation in blood coagulation. Therapeutic doses of thromboprophylaxis were unable to show significant benefit in randomised clinical trials, neither did anti-platelet medications [155-157]. Therefore, it might be intriguing to investigate whether the use of anti-inflammatory drugs could influence blood coagulation as well. Based on the above, it has some pathophysiological rationale that anti-IL-6 therapy could have beneficial indirect effects on the coagulation system: a hypothesis this study is aiming to answer.

VII.2.5. Strengths and limitations

Our study has potential strengths and limitations. To the best of our knowledge, this is the first registered clinical study on ClinicalTrials.gov to date on this topic. We will collect data prospectively in multiple centres to ensure external validity. All plasma and serum samples will be analysed by the same laboratory and each participating centre will use the same type of viscoelastic haemostasis assay to minimise inaccuracy. Regarding limitations, as there is no available data in the current literature that we could use for sample size calculation the proposed sample size of 30 patients may be too small. Furthermore, the time point chosen to assess the primary outcome (i.e., at 48 hours) is arbitrary due to the lack of published data on this topic. The use of other medications that could interfere with the blood coagulation may affect ClotPro® measurements. To minimise this, we will exclude patients who were submitted to fibrinolytic therapy, administration of factor products, fibrinogen, desmopressin, tranexamic acid, fresh frozen plasma or platelet concentrate. Finally, possible superinfections can also alter our results. Therefore, patients will be excluded due to any obvious sign of secondary infection (eg, positive blood culture).

VII.2.6. Clinical and research implications

Our results may provide further insight and understanding in the mechanisms of action of anti-IL-6 therapy and could provide data on the bedside routine use of VHA. In case of positive findings, our results could facilitate further research to unveil the crosstalk further between anti-inflammatory therapies and haemostasis.

VIII. Conclusion

In this thesis we aimed to evaluate the prognostic value of frailty in the context of the COVID-19 pandemic, with a particular focus on critically ill patients, and proposed a clinical trial protocol to further elaborate the effects of IL-6 antagonist therapy on haemostasis.

To investigate the prognostic value of frailty in COVID-19 we conducted a comprehensive systematic review and meta-analysis. Our results evidenced frailty as an independent predictor of adverse outcomes (notably 30-day and in-hospital mortality) in critically ill COVID-19 patients, irrespective of chronological age. Moreover, our results demonstrated indirectly, that mortality rate could not be improved by ICU level of care in patients living with frailty. Thus, frailty-based risk assessment should be implemented into guidelines for ICU admission.

In parallel, the second part of this work proposed a robust protocol for a prospective multicentre trial, through which we aim to investigate the effects of IL-6 receptor antagonist therapy in severe COVID-19 patients on haemostatic assays of these patients over time. And thus, we aim to address unresolved questions regarding the effects of immunomodulatory therapy on thromboinflammation.

Together, these components offer insights relevant both to clinical decision-making and to the evolving understanding of COVID-19 pathophysiology.

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Co-author certification

I, myself as a corresponding author of the following publication declare that the authors have no conflict of interest, and Máté Rottler Ph.D. candidate had significant contribution to the jointly published research. The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

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The publication relevant to the applicant's thesis:

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Co-author certification

I, myself as a corresponding author of the following publication declare that the authors have no conflict of interest, and Máté Rottler Ph.D. candidate had significant contribution to the jointly published research. The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

Sopron, 2025.08.06.

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