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

Improving clinical outcomes in critically ill COVID-19 patients

PhD thesis

Máté Rottler MD

Supervisor:

Prof. Zsolt Molnár MD, PhD, EDAIC

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1. Scientific metrics

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

2. List of 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

3. Introduction

The SARS-CoV-2 virus, which emerged in 2019, represented one of the most significant global public health crises in modern history. The rapid spread of the novel coronavirus and the high mortality associated with COVID-19 placed an unprecedented burden on healthcare systems. By the end of 2020, several million cases had been registered worldwide, leading to a substantial increase in global mortality rates.

During the pandemic, intensive care units around the world faced severe capacity shortages. The relative lack of organ support equipment and adequately trained personnel directly impacted the quality of patient care and, consequently, survival rates. Fair and ethical triage of patients to the appropriate levels of care became critically important. Therefore, major scientific efforts were directed towards identifying prognostic factors to enable the optimal allocation of limited resources.

Among the risk factors for severe COVID-19 are advanced age and frailty, along with male sex, obesity, and the presence of chronic comorbidities. Early large-cohort studies showed that individuals over the age of 65 were disproportionately represented among those with severe or fatal outcomes. However, advanced age alone could not sufficiently explain this disproportionate mortality. As a result, frailty came into focus as a complex condition that reflects the reduction of an individual's physiological, cognitive, and functional reserves. Although frailty is more common in the elderly, it is not exclusively linked to age but develops as a result of cumulative deficits, influenced by chronic diseases, lifestyle factors, and genetic predisposition, progressing at varying rates in different individuals. As ICU capacities became overwhelmed, the need for objective frailty assessment grew, including its incorporation into patient triage decisions. However, in this extraordinary situation, there was little scientific evidence validating the prognostic value of frailty.

Severe COVID-19 is largely driven by an excessive activation of the immune system. The close interconnection and parallel activation of the immune and coagulation cascades lead to the phenomenon known as thromboinflammation, which contributes not only to lung injury but also to damage of the cardiovascular system and other organ systems. Understanding this pathophysiology, together with the results of large clinical trials, led to the introduction of immunomodulatory therapies such as IL-6 receptor antagonists in the treatment of severe COVID-19. IL-6 plays a crucial role as a connecting point between the immune and coagulation systems. However, the effect of IL-6 antagonists on the coagulation cascade in this hypercoagulable state remains insufficiently understood.

4. Objectives

The primary aim of this thesis is to explore the factors influencing clinical outcomes in patients with severe COVID-19, with a particular focus on frailty as a prognostic indicator and to explore the effects of IL-6 antagonist therapy on blood coagulation.

Therefore, this thesis has two main objectives:

1. To investigate the association between frailty and mortality, ICU admission, and length of hospital stay in COVID-19 patients through a systematic review and meta-analysis
2. To develop a protocol for a prospective, multicentre, observational study assessing the effects of IL-6 antagonist therapy on coagulation parameters

5. Methods: The studies

5.1. 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

5.1.1. Introduction

Frailty is a state associated with reduced physiological reserve, resulting in increased vulnerability to stressors. Frail patients are at a higher risk of adverse outcomes due to their diminished ability to restore homeostasis. Frailty develops as a consequence of the accumulation of deficits over a lifetime, with the rate of accumulation varying between individuals. Its development is primarily influenced by genetic, environmental, and lifestyle factors.

The 9-point Clinical Frailty Scale (CFS) was developed by Rockwood and colleagues as a simple tool with good predictive value. The scale assesses functional independence, such as mobility, the use of walking aids, or the need for assistance in performing activities of daily living (*Figure 1*). It integrates morbidity as well as the progressive decline in physical and cognitive functions into a single phenotype. CFS assessment should be based on the patient's baseline health status at least two weeks prior to the onset of the acute illness.

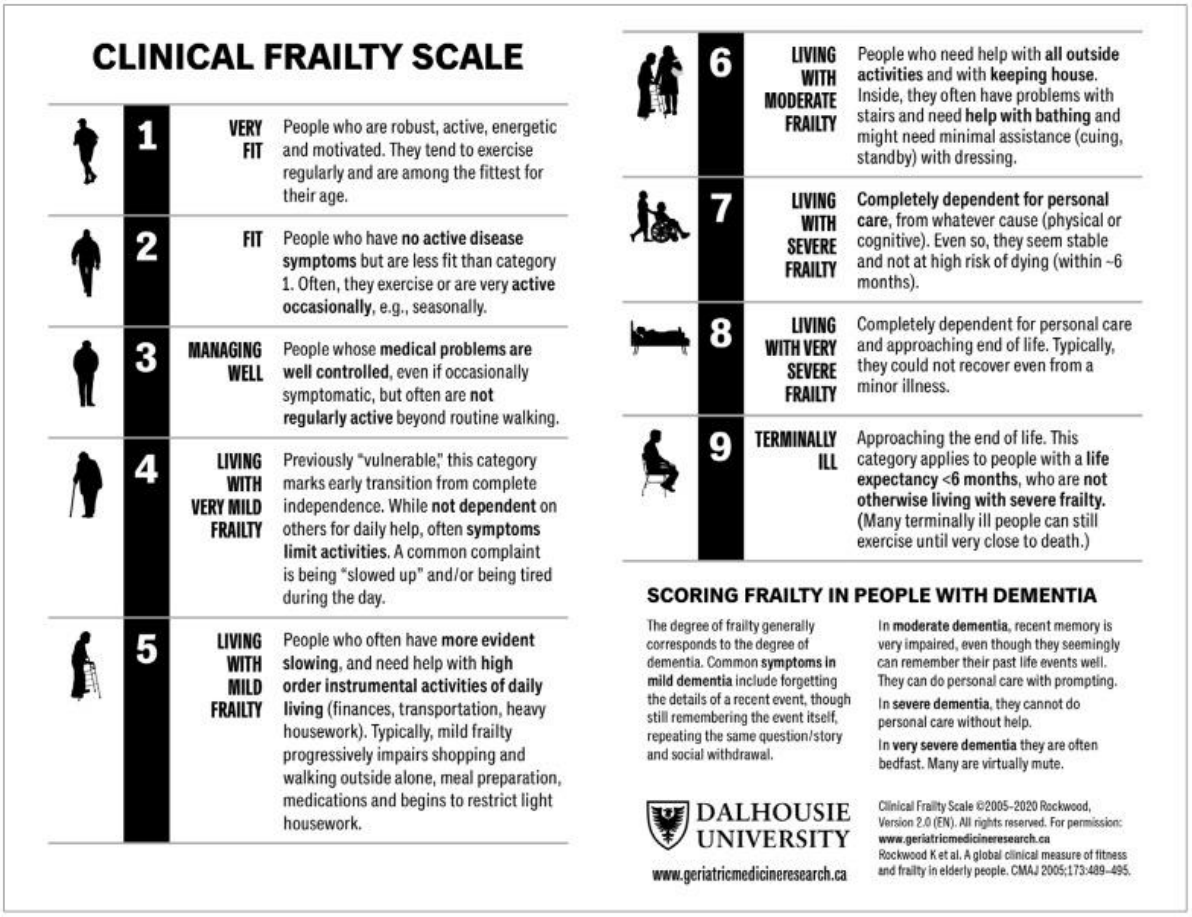

Figure 1: *The Clinical Frailty Scale: Assessment of different levels of frailty.*

The Hospital Frailty Risk Score (HFRS) was developed to automatically estimate frailty risk in older patients based on routinely collected hospital data, particularly using ICD-10 codes.

The Multidimensional Prognostic Index (MPI) is primarily used in geriatrics as part of a comprehensive geriatric assessment. It has been validated for predicting both short- and long-

term outcomes. Although it is a valuable tool in geriatric care, its applicability in other fields, particularly in intensive care, is limited.

During the COVID-19 pandemic, frailty was incorporated into triage protocols in several healthcare systems and countries, particularly to guide decisions regarding ICU admission or the initiation of mechanical ventilation. The aim of our research was to provide a comprehensive summary focusing on the association between frailty and in-hospital or 30-day mortality, ICU admission, and length of hospital stay.

5.1.2. Methods

5.1.2.1. *Protocol registration and reporting*

The study protocol was prospectively registered in the PROSPERO database under the registration number CRD42021241544. There were no deviations from the protocol. Our results were reported in accordance with the PRISMA guidelines.

5.1.2.2. *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. 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.

5.1.2.3. *Search and selection*

The systematic search was conducted until September 24, 2021, in the following databases: MEDLINE (via PubMed), Embase, CENTRAL, Web of Science, and Scopus, using a search key constructed based on the PECO format.

Two independent reviewers screened the titles, abstracts, and then full texts according to predefined eligibility criteria. Any disagreements were resolved by a third reviewer.

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.

5.1.2.4. *Risk of bias*

Risk of bias was assessed independently by two researchers in parallel, following the recommendations of the Cochrane Collaboration, using the Quality in Prognosis Studies (QUIPS) tool.

5.1.2.5. *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.

For dichotomous outcomes, odds ratios (ORs) with their 95% confidence intervals (CI) were calculated from the original raw data of the articles. For continuous outcomes, weighted mean differences (WMDs) with 95% CI were calculated from the original raw data of the articles.

We used the random effect model by DerSimonian and Laird. 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. The potential for a "small study effect", including publication bias, was examined by visual inspection of funnel plots.

5.1.3. Results

5.1.3.1. *Selection and characteristics of included studies*

The systematic search yielded 3640 records. 54 studies were included in the qualitative and 42 in the quantitative synthesis (*Fig. 2)*.

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. Most studies enrolled patients over 65 years.

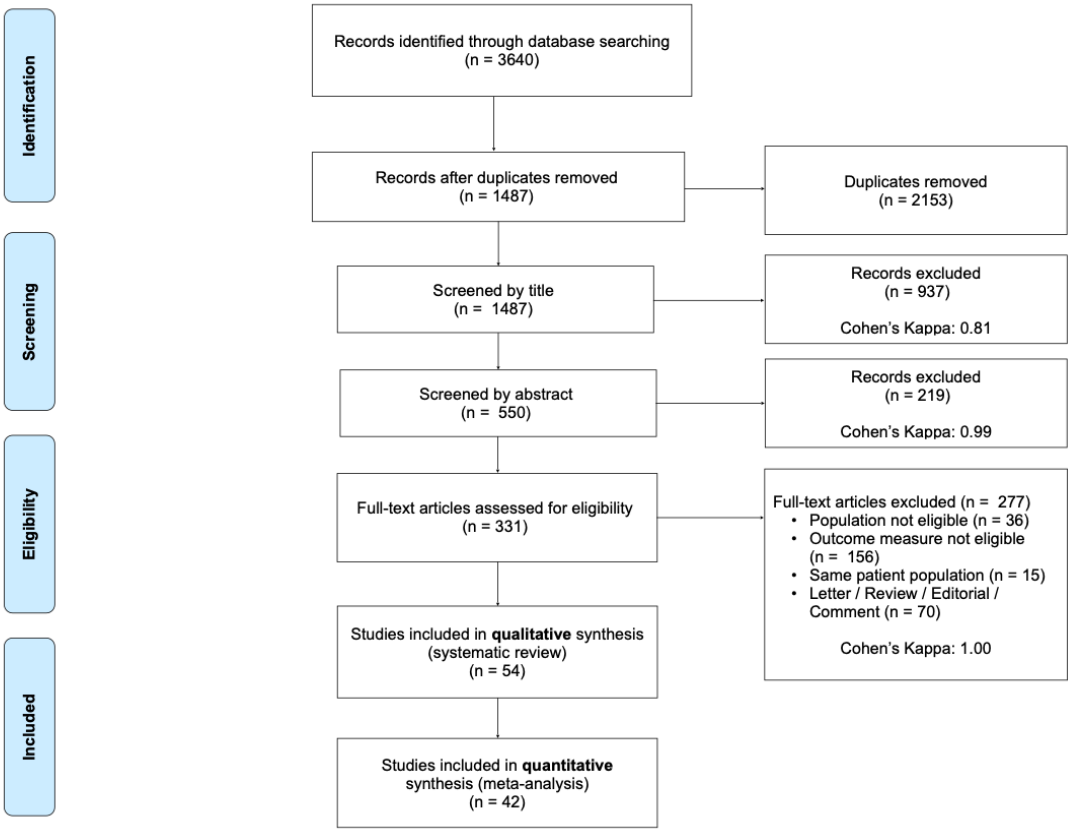

Figure 2: *Flowchart of study selection according to the PRISMA Statement*

5.1.3.2. *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.

5.1.3.3. *Mortality*

Frailty measured with the Clinical Frailty Scale

46 studies reported on CFS as a measure of frailty. 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. 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.

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 (CFS 1–3) (Fig. 3).

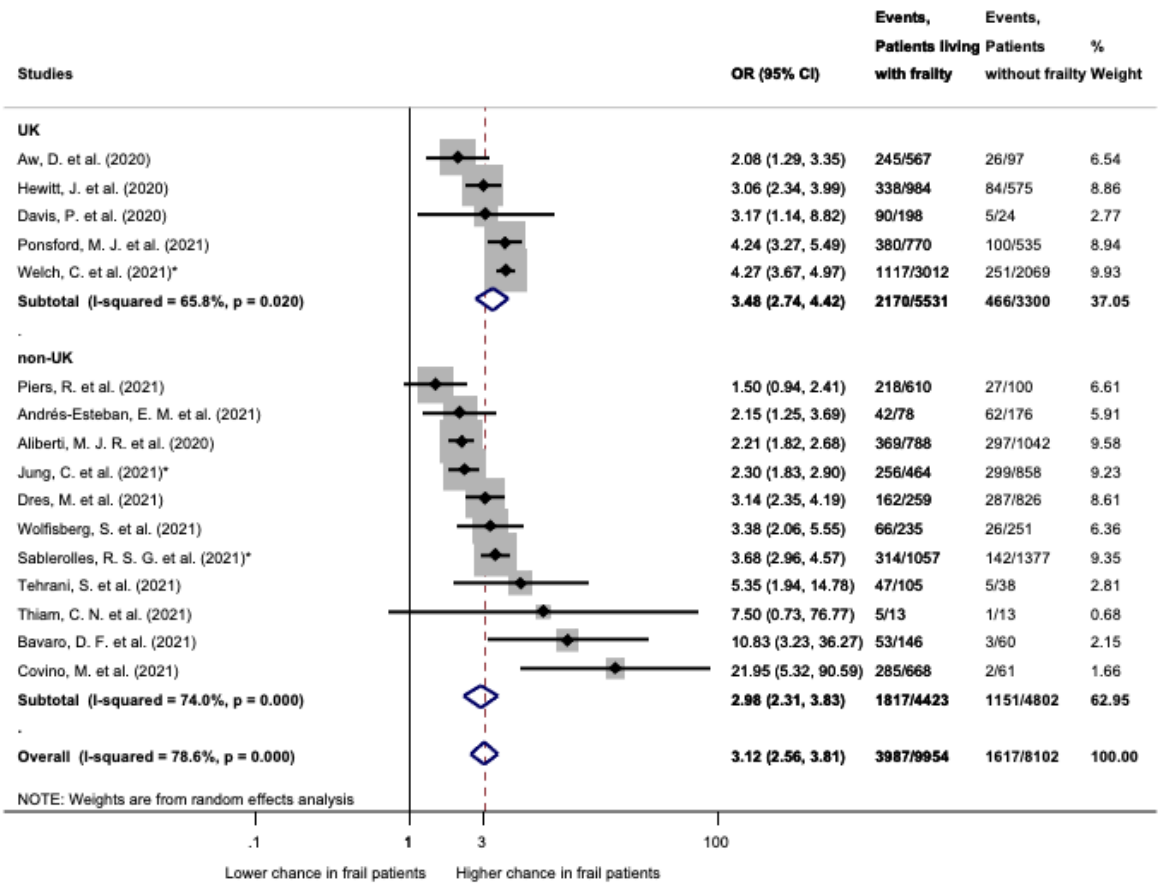

Figure 3: *Mortality in patients with frailty (CFS 4–9) compared to not frail (CFS 1–3)*

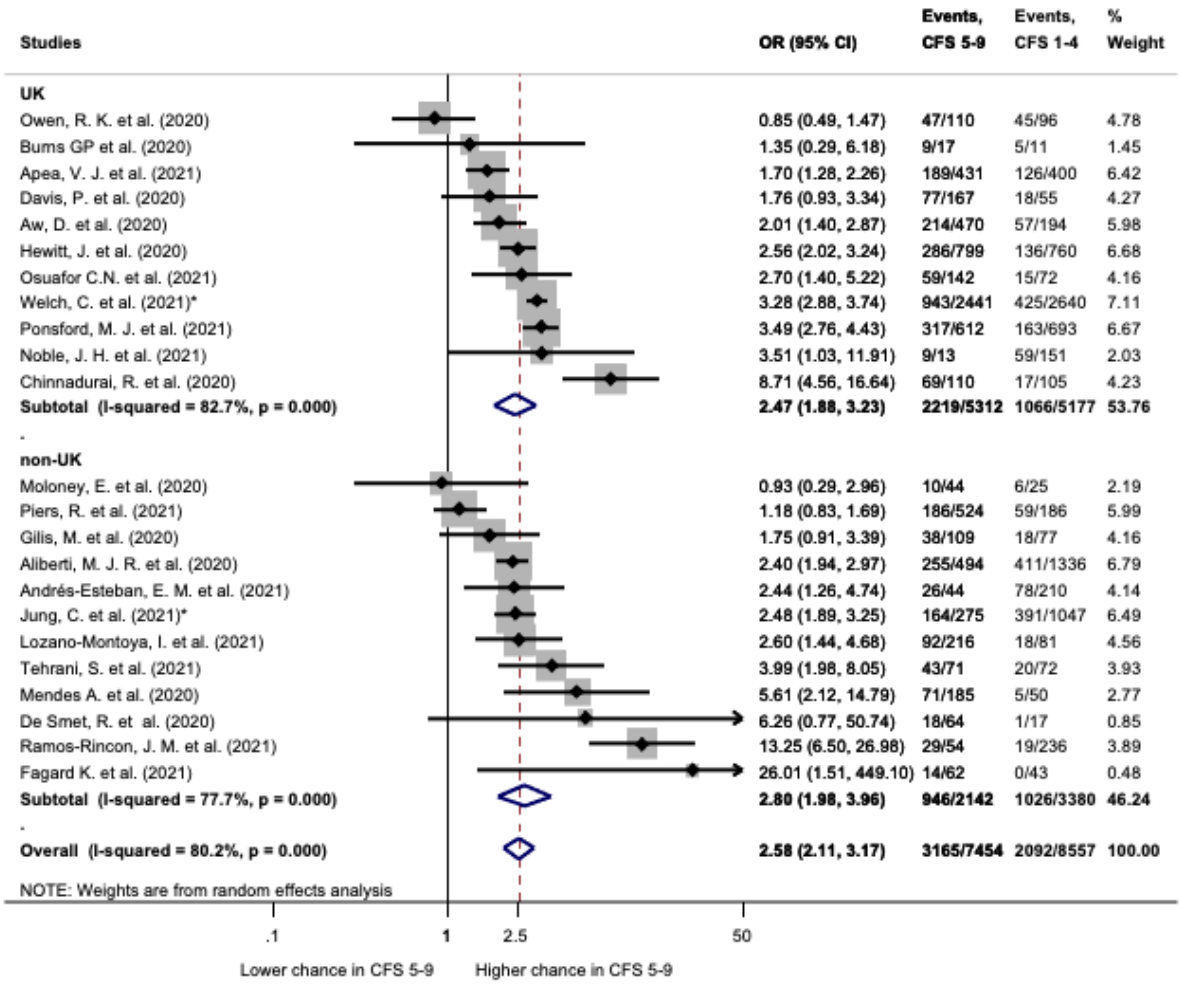

Figure 4: *Mortality in patients with CFS 5–9 compared to CFS 1–4.*

In order to get a more thorough picture, studies comparing CFS 1–4 with CFS 5–9 were also quantitatively analysed. 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*).

Nineteen studies reported the mean or median frailty in survivors and non-survivors, of which 12 were included in quantitative synthesis. Non-survivors generally scored significantly higher using the CFS than survivors (overall WMD: 1.21; CI 0.83–1.59).

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 (England and Turkey), including over 75,000 patients. The third study was a hospital cohort study from Spain. 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).

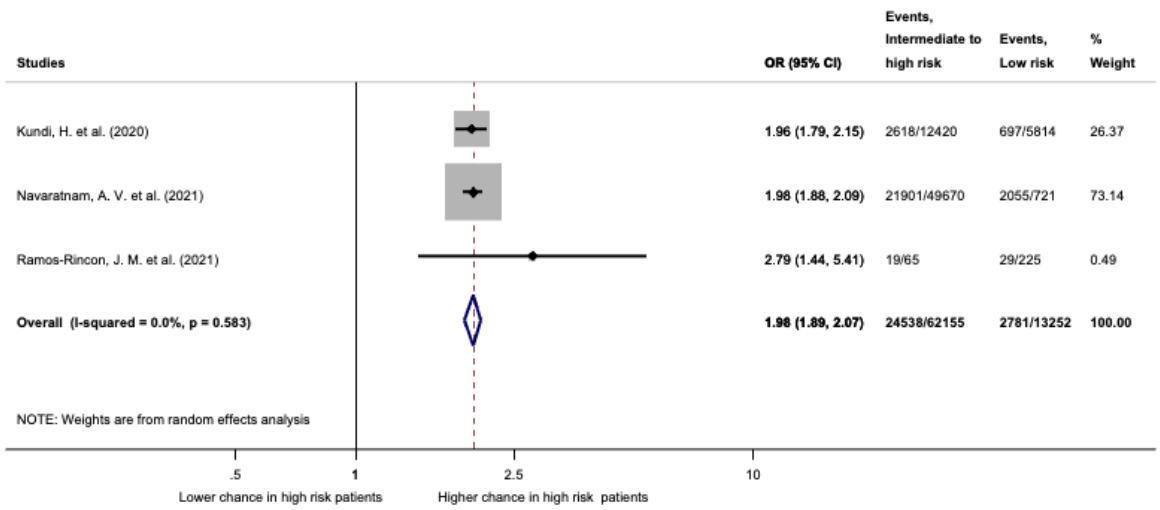

Figure 5: *Mortality and frailty assessed by the Hospital Frailty Risk Score.*

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 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).

5.1.3.4. *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).

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. In this group, frailty did not significantly reduce the chance for ICU admission (OR: 0.83; CI 0.63–1.09) (*Fig. 6*).

In another quantitative analysis of studies, we examined association of ICU admission in a CFS 5–9 compared CFS 1–4. In the quantitative synthesis, 6 studies could be included. 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).

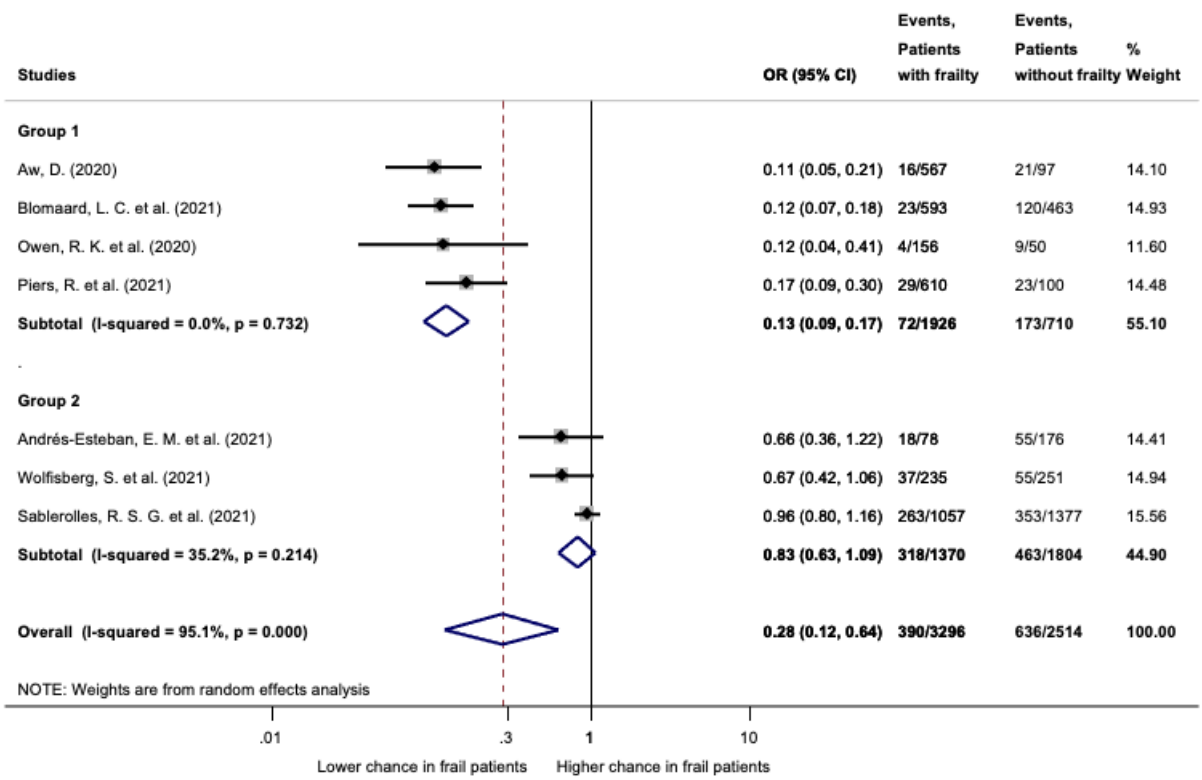

Figure 6: *ICU admission in patients with frailty indicated by CFS 1–3 vs 4–9*

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

5.1.3.6. *Publication bias*

Visual examination of funnel plots and Eggers' tests did not show small-study effect for any examined outcomes, but one. On the funnel plot of ICU admission CFS 1–3 vs 4–9 strong asymmetry can be observed, which may be due to publication bias.

5.1.4. 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. 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. Therefore, prolonged, advanced organ support might be regarded as medically futile in those cases whose chances are extremely limited for survival. 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. A potential alternative is the assessment of frailty.

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. 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.

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.

5.2. 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

5.2.1. Introduction

The SARS-CoV-2 virus has highlighted the critical importance of the interplay between the immune system and the coagulation cascade. From a pathophysiological perspective, in severe COVID-19, the thromboinflammatory process is triggered by a dysregulated immune response. This response activates both the inflammatory and coagulation systems, either directly through immune mediators or indirectly via endothelial cell injury. Together, these mechanisms lead to a disruption of haemostatic balance, characterized by a pronounced procoagulant state.

One of the key proinflammatory cytokines involved in the crosstalk between the immune and coagulation systems is interleukin-6 (IL-6). Elevated IL-6 levels contribute to haemostatic imbalance by inducing thrombocytosis, enhancing platelet activation and aggregation, and exerting an inhibitory effect on the fibrinolytic system.

Based on this understanding, IL-6 antagonists were introduced into the therapeutic recommendations for severe COVID-19. However, very few studies have evaluated the effects of these agents on the coagulation system using viscoelastic testing methods. Therefore, this study aims to provide further essential data to improve the understanding of their precise mechanisms of action.

5.2.2. Objectives

- 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.

5.2.3. Methods and Analysis

5.2.3.1. *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 1: *Type and main characteristics of the participating ICUs*

Inclusion criteria	Exclusion criteria
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 indicates 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 • 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 2: *Eligibility criteria.*

This is a prospective, multi-centre observational study of critically ill patients with COVID-19 admitted to the intensive care unit. 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 1*. 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.

5.2.3.2. *Patient population*

Inclusion and exclusion criteria are summarised in *table 2*. 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.

5.2.3.3. *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 and current status will be recorded. Clinical and laboratory parameters, such as blood pressure, 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. 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.

5.2.3.4. *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 (T_2) 5 days (T_3) and 7 days (T_4) later. *Table 3* 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, FIB-test, IN-test, TPA-test, RVV-test and ECA-test will be used. CT, CFT, ∝-Angle, MCF, ML will be recorded for EX-test, FIB-test, IN-test, RVV-test. LT, LOT, ML, CLI-30, CLI-45 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 3: *Timeline of the assessment of inflammatory and coagulation parameters relative to the administration of IL-6.*

The results of the routine laboratory tests such as the whole blood count, inflammatory parameters will be collected every day.

Blood sample will be drawn for further analysis in central laboratory to measure the level of IL-6 and syndecan-1, plasminogen, plasminogen activator inhibitor/PAI-1, von Willebrand factor antigen and activity, and factor VIII.

5.2.3.5. *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).

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

- Change of the fibrinolytic system before and after immunomodulation therapy.
- Change in blood coagulation parameters that evaluate hypercoagulable state before (T_0) and after immunomodulation therapy ($T_{1,2,3,4}$)
- Correlation between inflammatory and blood coagulation parameters.
- Correlation between biomarkers of endothelial injury and blood coagulation parameters.

5.2.3.6. *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, after which an interim analysis and final sample size calculation 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). The collected data will be evaluated using descriptive statistical methods.

5.2.3.7. *Ethical considerations*

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.

5.2.4. 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. 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. Besides conventional laboratory parameters, the coagulation disorder caused by COVID-19 was described using VHA tests as well. 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.

The level of IL-6 correlates with the disease severity in patients with COVID-19. Therefore, the rationale of using IL-6 antagonist to decrease the severity of inflammatory response in COVID-19. The benefits of immunomodulation have been shown in critically ill patients with COVID-19 and this indication is included in WHO living guidelines.

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.

5.2.5. 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. 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. 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).

5.2.6. 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.

6. 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.