ABSTRACT

Introduction  Hypercoagulation is one the main features of COVID-19. It is induced by the hyperinflammatory response that shifts the balance of haemostasis towards pro-coagulation. Interleukin-6 (IL-6) antagonist therapy has been recommended in certain subgroups of critically ill patients with COVID-19 to modulate inflammatory response. The interaction between immune response and haemostasis is well recognised. Therefore, our objective is to evaluate whether the modulation of the inflammatory response by IL-6 antagonist inflicts any changes in whole blood coagulation as assessed by viscoelastic methods in critically ill patients with COVID-19.

Methods and analysis  In this prospective observational study, we are going to collect data on inflammatory parameters and blood coagulation using the ClotPro® device. The primary outcome is the change of the fibrinolytic system measured by the Lysis Time and Lysis onset time before and after immunomodulation therapy. Data will be collected before the IL-6 antagonist administration at baseline (T₀) then after 24, 48 hours, then on day 5 and 7 (T₁, T₄, respectively). Secondary outcomes include changes in other parameters related to inflammation, blood coagulation and biomarkers of endothelial injury.

Ethics and dissemination  Ethical approval was given by the Medical Research Council of Hungary (1405-3/2022/EÜG). All participants provided written consent. The results of the study will be disseminated through peer-reviewed journals.

Trial registration number  NCT05218369; Clinicaltrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, observational, multicentre study investigating the relationship between blood coagulation and treatment with interleukin-6 (IL-6) antagonists in patients with COVID-19.
⇒ The participating sites use the same viscoelastic haemostasis assay device (ClotPro®) and special coagulation tests will be analysed in the same laboratory to reduce the possibility of heterogeneity and inaccuracy.
⇒ There will be no control group to compare the effects of IL-6 antagonists.
⇒ The time point chosen to assess the primary outcome (ie, at 48 hours) is arbitrary due to the lack of published data on this topic.
⇒ Currently there is also insufficient data in the literature to perform pro forma sample size calculation, hence there is a risk that the study will be underpowered.

INTRODUCTION

The emerging SARS-CoV-2 virus has shed new light on the cross-talk between the immune and the blood coagulation system. From the pathophysiological standpoint in COVID-19 infection, the thrombo-inflammatory 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. 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. 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.

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.6 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.7

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).8 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.9

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.10 11 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.

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:
1. To assess the changes of the coagulation profile and the fibrinolytic system by VHA parameters before and after immunomodulation with IL-6 antagonist administration.
2. To test the associations between coagulation, endothelial damage and inflammatory parameters before and after IL-6 antagonist therapy.

METHODS AND ANALYSIS
Study design and setting
This is a prospective, multi-centre observational study of critically ill patients with COVID-19 admitted to the ICU. Currently, there are four multidisciplinary 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. 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.

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.

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 Scale12 13 and current status will be recorded. Clinical and laboratory parameters, such as blood pressure (systolic, diastolic), heart rate, peripheral capillary oxygen saturation (SpO₂), 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.

Laboratory data and VHA
Blood samples necessary for laboratory analysis and VHAs will be obtained at the same time, on the day of inclusion (T₀) and then 24 hours (T₁), 48 hours (T₂), 5 days (T₃) and 7 days (T₄) 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 (CaCl2 recalculates 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), $\infty$-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.

The results of the routine laboratory tests such as the whole blood count, inflammatory parameters (procalcitonin, C reactive protein, ferritin), clinical biochemistry (creatinine, 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 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 $-80^\circ$C. All collected samples will be analysed in the same laboratory.

Outcomes

The primary outcome is the change of the fibrinolytic system measured by the LT and LOT before ($T_0$) and after immunomodulation therapy ($T_7$). 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:

---

### Table 2: Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Adults (>18 years old) | The patient or his legal guardian does not sign the consent |
| Clinical diagnosis of SARS-CoV2 infection with rTPCR confirmation | Presence of any condition or drug in the medical history that can lead to immunosuppression |
| Disease severity with the indication of immunomodulation therapy with interleukin-6 antagonist: acute respiratory failure that requires invasive, noninvasive ventilation, Noninvasive $O_2$ therapy or high flow nasal oxygen therapy with the following parameters: $FiO_2 > 0.4$, flow $> 30$ L/min and CRP $> 75$ mg/L | The number of thrombocytes lower than $50 \times 10^9$/L |
| More than 120 hours passed between the admission to the ICU and the administration of an interleukin-6 antagonist | 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) |
| The patient had previously been administered one of the following immunomodulating drugs: anakinra, tocilizumab, sarilumab | The number of thrombocytes lower than 50×10^9/L |
| The number of thrombocytes lower than 50×10^9/L | The patient had previously been administered one of the following immunomodulating drugs: anakinra, tocilizumab, sarilumab |
| Diagnosis of infection with rtPCR confirmation | The patient had previously been administered one of the following immunomodulating drugs: anakinra, tocilizumab, sarilumab |

### Table 3: Timeline of the assessment of inflammatory and coagulation parameters relative to the administration of IL-6 antagonist

| Day | Conventional laboratory parameters | ClotPro® tests | Blood sample |
|-----|-----------------------------------|----------------|--------------|
| 0   | Inflammatory parameters, clinical biochemistry and conventional coagulation parameters | EX, IN, FIB, TPA, RVV, ECA tests | Plasma, serum |
|     | Administration of IL-6 antagonist  |                |              |
| 24 hours | Inflammatory parameters, clinical biochemistry and conventional coagulation parameters | EX, IN, FIB, TPA, RVV, ECA tests | Plasma, serum |
| 48 hours | Inflammatory parameters, clinical biochemistry and conventional coagulation parameters | EX, IN, FIB, TPA, RVV, ECA tests | Plasma, serum |
| 5 days  | Inflammatory parameters, clinical biochemistry and conventional coagulation parameters | EX, IN, FIB, TPA, RVV, ECA tests | Plasma, serum |
| 7 days  | Inflammatory parameters, clinical biochemistry and conventional coagulation parameters | EX, IN, FIB, TPA, RVV, ECA tests | Plasma, serum |

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.
1. Change of the fibrinolytic system assessed by VHA and measured by the plasminogen, PAI-1 before (T₀) and after immunomodulation therapy (T₁,₂,₃,₄).
2. Change in blood coagulation parameters that evaluate hypercoagulable state before (T₀) and after immunomodulation therapy (T₁,₂,₃,₄) measured by Clotpro® device assays comparing: CT, CFT, MCF.
3. 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).
4. 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.

**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.), after which an interim analysis and final sample size calculation (power: 80%, type I error: 5%) for the primary endpoint (change in LT. between T₀) 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 (Q₁−Q₃). 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 the 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.

**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.

**Patient and public involvement**

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

**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/EUG. As this is not an interventional study, therefore, 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.

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.

**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, 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. Later Iba et al proposed the following criteria: (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. 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.22

The level of IL-6 correlates with the disease severity in patients with COVID-19.23 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.24 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.25 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.21 24 26 27

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.28–30 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.

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 in 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 (ie, 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).

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.

Author affiliations

1Centre for Translational Medicine, Semmelweis University, Budapest, Hungary
2Selye János Doctoral College for Advanced Studies, Semmelweis University, Budapest, Hungary
3Department of Anaesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary
4Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary
5Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary
6Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary
7Department of Anaesthesiology and Intensive Therapy, Poznan University of Medical Sciences, Poznan, Poland
8Soproni Erőszámt Teaching Hospital and Rehabilitation Institute, Sopron, Hungary
9Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
10Department of Anaesthesiology and Critical Care, University of Pécs, Pécs, Hungary
11Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary
12Department of Anaesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary
13Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
14Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
15Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
16Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
17Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
18Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
19Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
20Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
21Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
22Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
23Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
24Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
25Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
26Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
27Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
28Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
29Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary
30Department of Anaesthesiology and Critical Care, Semmelweis University, Budapest, Hungary

Contributors EHK, MR: planning of the study and drafting of the manuscript; LS: writing of the statistical analysis plan; KO, FD, PH: methodological supervision, ZM: methodological supervision and revision of the manuscript; TK: original idea, planning of the study and critical revision of the manuscript. All of the authors read and approved the final manuscript. Contributorship statement: EHK and MR contributed equally to this study.

Funding This work was supported by the Hungarian National Research, Development And Innovation Office (K 138816).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Emke Henrietta Kovács http://orcid.org/0000-0002-6417-2296
Klementina Ocskay http://orcid.org/0000-0001-5843-2506
Peter Hegyi http://orcid.org/0000-0003-0389-7259
Zsolt Molnár http://orcid.org/0000-0002-1468-4058

REFERENCES

1. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020;8:e46–7.
2. Llitjos J, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18:1743–6.
3 Levy JH, Iba T, Olson LB, et al. COVID-19: thrombosis, thromboinflammation, and anticoagulation considerations. *Int J Lab Hematol* 2021;43 Suppl 1:29–35.

4 Cuker A, Tseng EK, Nieuwlaat R, et al. American society of hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. *Blood Adv* 2022;6:4915–23.

5 National Institute of Health COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19, 2022. Available: https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/ [Accessed 23 Aug 2022].

6 Nishimoto N, Kishimoto T, Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006;2:619–26.

7 Hou T, Tieu BC, Ray S, et al. Roles of IL-6-gp130 signaling in vascular inflammation. *Curr Cardiol Rev* 2008;4:179–92.

8 Bester J, Pretorius E. Effects of IL-1, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity. *Sci Rep* 2016;6.

9 D’Alessandro A, Thomas T, Dzieciatkowska M, et al. Serum proteomics in COVID-19 patients: altered coagulation and complement status as a function of IL-6 level. *J Proteome Res* 2020;19:4417–27.

10 COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines National Institutes of Health; 2022. Available: https://www.covid19treatmentguidelines.nih.gov/ [Accessed 18 Aug 2022].

11 World Health Organization. Therapeutics and COVID-19: living guideline; 2021. WHO/O纠错n/COVID-therapeutics/2021.2 [Accessed 6 Aug 2021].

12 Rockwood K, Song X, MacKnight C, et al. Impaired fibrinolysis in critically ill COVID-19 patients. *Br J Anaesth* 2021;126:390–8.

13 Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. *Can Geriatr J* 2020;23:254–9.

14 Bachier M, Bosch J, Stiel DP, et al. Impaired fibrinolysis in critically ill COVID-19 patients. *Br J Anaesth* 2021;126:390–8.

15 Hungarian Ministry of Human Resources (Emberi Erőforrások Minisztériuma). Basics of the treatment of confirmed COVID-19 infected adults (ígyzolt COVID-19 fertőzött felhőitkek kezelésének alapja). In: *Handbook for the prevention and treatment of new coronavirus (SARS-CoV-2) infections (COVID-19) identified in 2020 a 2020.* Éven azonosított új koronavírus (SARS-CoV-2) okozta fertőzések (COVID-19) megelzésének és terápiájának kezikönyve (IV/10948-8/2020/EGPOL); 2022. https://koronavirusz.gov.hu/sites/default/files/sites/default/files/imce/magyar_koronavirus_kezikonyv_igazolt_covid-19_betegek_kezelese_cimu_fejezet_-_.2021.november.pdf

16 von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ* 2007;85:867–72.

17 Darif D, Hammi I, Kihel A, et al. The pro-inflammatory cytokines in COVID-19 pathogenesis: what goes wrong? *Microb Pathog* 2021;153:104799.

18 Cortegiani A, Ippolito M, Greco M, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology* 2021;27:52–66.

19 Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7.

20 Iba T, Warkentin TE, Thachil J, et al. Proposal of the definition for covid-19-associated coagulopathy. *J Clin Med* 2021;10:191.

21 Bareille M, Hardy M, Douxfils J, et al. Viscoelastic testing to assess hemostasis of COVID-19: a systematic review. *J Clin Med* 2021;10:10.

22 Shen L, Tabaei S, Ivascu N. Viscoelastic testing inside and beyond the operating room. *J Thorac Dis* 2017;9:3299–308.

23 Liu Z, Li J, Chen D, et al. Dynamic interleukin-6 level changes as a prognostic indicator in patients with COVID-19. *Front Pharmacol* 2020;11:1093.

24 REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–502.

25 Rubbert-Roth A, Furst DE, Nebesky JM, et al. A review of recent advances using tocilizumab in the treatment of rheumatic diseases. *Rheumatol Ther* 2018;5:21–42.

26 Tleyjeh IM, Kashour Z, Damaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. *Clin Microbiol Infect* 2021;27:215–27.

27 Avabi O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *The Lancet* 2021;397:1637–45.

28 Ortega-Paz L, Galli M, Capodanno D. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically non-critically ill patients with covid-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother* 2021.

29 Salah HM, Mehta JL. Meta-analysis of the effect of aspirin on mortality in COVID-19. *Am J Cardiol* 2021;142:158–9.

30 Wang Y, Ao G, Nasr B, et al. Effect of antiplatelet treatments on patients with COVID-19 infection: a systematic review and meta-analysis. *Am J Emerg Med* 2021;43:27–30.