Appendix

Impact on coagulation due to coronavirus (2020)

Table for included primary studies - Question 1: What scientific studies are there on the impact on coagulation during infection with SARS-CoV 2, Sars-CoV-1 or Mers-CoV?

Author Year Study design Setting	Population	Intervention and control treatments	Outcome	Results	Aims Conclusions	Risk of bias Limitations
Lodigiani et al 2020 **Design:** Retrospective cohort study without comparison group **Setting:** One university hospital in Milan, Italy	Patients with covid-19 who were consecutive admitted to a university hospital in Milan between 13 February to 10 April 2020. Median age=66 % male=68%	**Participants:** n=388 ICU: n=61 General ward: n=327 **Thromboprophylaxis**: 61 (100%) patients in the ICU and 246 (75%) patients in the general ward received thromboprophylaxis	**Primary outcome:** Thromboembolic complications, such as venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS)/myocardial infarction (MI) **Secondary outcome:** Overt disseminated intravascular coagulation (DIC)	**Thromboembolic events**: Occurred in 28 of 362 closed cases for a rate of 7.7% (95% CI, 5.4% to 11.0%). **Overt DIC**: A total of 8 (2.1%) patients met the laboratory criteria for overt DIC Also presented D-dimer levels between survivors and non-survivors among hospitalization	**Aim**: To describe the rate of venous and arterial thromboembolic complications in hospitalized patients with covid-19 **Conclusion**: Hospitalized patients with covid-19 were characterized by substantial in-hospital mortality and a high rate of thromboembolic complications. Rapidly increasing D-dimer levels were observed in non-survivors, reflecting the inflammatory and procoagulant state of covid-19. The high number of arterial and venous thromboembolic events diagnosed within 24 h of admission and the high rate of positive VTE imaging tests suggest that there is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory covid-19 patients.	Moderate risk of bias

Zhang et al 2020 **Design:** Nonrandomized retrospective cohort study with a comparison group **Setting:** One hospital in Wuhan, China	Adult patients with covid-19 were enrolled in Wuhan Asia General Hospital from 12 January to 15 March 2020. Median age=62 % male=49.3%	**Participants**: n=343 Participants were stratified by D-dimer level	**Primary outcome:** Mortality	**Mortality:** D-dimer <2.0 µg/ml: 1 of 276 patients (0.4%) died D-dimer >2.0 µg/ml: 12 of 67 patients (15.8%) died **Optimum cut-off value:** D-dimer: 2.0 µg/ml with a sensitivity of 92.3% and a specificity of 83.3%. D-dimer: C-index 0.883 (95% CI, 0.842 to 0.916) **Predictive value:** D-dimer level ≥2.0µg/ml was the significant predictor of death after adjusting for gender, age and underlying diseases (HR:22 .4; 95% CI, 2.86 to 175.7, p=0.003)	**Aim:** Evaluate whether elevated D-dimer levels could predict mortality in patients with covid-19. **Conclusion:** D-dimer on admission greater than 2.0 µg/mL could effectively predict in-hospital mortality in patients with covid-19, which indicated D-dimer could be an early and helpful marker to improve management of covid-19 patients.	Moderate risk of bias
Zou et al 2020 **Design:** Nonrandomized retrospective cohort study with a comparison group **Setting:** One hospital in Shanghai	Adult patients with confirmed covid-19 who were admitted to the Shanghai Public Health Clinical Center between 20 January to 24 February 2020. Median age=51 % male=52%	**Participants**: n=303 patients of 324 were included in the study The patients were then put into two groups in terms of the severity of the disease **Mild:** 277 participants with mild (n=1) or moderate covid-19 (n=276) were assigned to the "mild group"	**Primary outcomes.** Coagulation parameters, such as PT, D-dimer, fibrinogen, abnormal APTT, FDP and INF	**Abnormal coagulation parameters** (Severe: 100% vs. mild: 66.1%) 209 (69%) of the participants had abnormal coagulation parameters in a total of at admission **Proportion of abnormal fibrinogen:** (Severe: 80.8% vs. mild: 62.8%), **Proportion of abnormal D-dimer**: (Severe: 80.8% vs. mild: 39.0%), **Proportion of abnormal APTT:** (Severe: 34.6% vs. mild: 20.6%), **Proportion of abnormal PT:** (Severe: 38.5% vs. mild: 16.6%),	**Aim:** To investigate the correlation between coagulopathy and covid-19 by comparing baseline coagulation functions of patients with different disease severity. **Conclusion:** That coagulopathy is common among covid-19 patients and that DIC-related parameters are significantly elevated in patients with severe cases compared to those with mild cases	Moderate risk of bias

		Severe: 26 participants with severe (n=10) or critical (n=16) covid-19 were assigned to the "severe group"		**Proportion of abnormal FDP:** (Severe: 19.2% vs. mild: 5.1%)		
Gao et al 2020 **Design:** Nonrandomized retrospective cohort study with a comparison group. **Setting:** One hospital in china.	Adults patients with confirmed covid-19 who were admitted to the Fuyang Second People's Hospital between 23 January and 2 February 2020. Mean age=44±12 % male=61%	**Participants:** n=43 patients were included in the study The patients were then put into two groups in terms of the severity of the disease **Mild:** 28 patients **Severe:** 15 patients	**Primary outcomes:** White blood cell (WBC) count, lymphocyte count (LYM), mononuclear count (MONO), neutrophils count (NEU), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose (GLU), urea, creatinine (Cr), cystatin (Cys-c), uric acid (UA), C-reactive protein (CRP), D-dimer, thrombin time (TT), PT, FIB, APTT and Procalcitonin (PCT)	**Clinical laboratory data:** GLU, CRP, IL-6, TT, FIB, and D-dimer were significantly higher in the severe group compared to the mild group. WBC, LYM, NEU, MONO counts were not significantly different between the severe group and the mild group. **Predictive values:** **IL-6**: AUC: 0.795 (95% CI, 0.645 to 0.903; p<0.000) **D-dimer:** AUC: 0.750 (95% CI, 0.595 to 0.869; p=0.005) **D-dimer + IL-6:** AUC: 0.840 (95% CI, 0.697 to 0.934; p<0.000) AUC of TT, GLU, CRP, and FIB were below 0.750. **Optimal cut-off values:** **IL-6** 24.3 µg/L. Sensitivity of 73.3% and a specificity of 89.3% **D-dimer:** 0.28 µg/L, Sensitivity of 86.7% and a specificity of 82.1% **IL-6 or D-dimer:** Sensitivity: 93.3, Specificity: 75.0 **IL-6 and D-dimer:** Sensitivity: 66.7, Specificity: 96.4	**Aim**: Assess the hematological characteristics of covid-19 patients. Also, determine the correlation between clinical laboratory data and the severity of covid-19 in adult patients. Moreover, determine the predictive value of clinical laboratory data for the severity of covid-19 **Conclusion:** In conclusion, our findings suggest that IL-6 and d -D levels can be used to estimate the severity of covid-19. If necessary, the levels of IL-6 and d-D should be measured, as they can help diagnose the severity of adult covid-19 patients	Moderate risk of bias

Chen et al 2020 **Design:** Retrospective case series **Setting:** One hospital in Wuhan, China	Patients with confirmed covid-19 who either was dead or had recovered (13 January – 12 February 2020) at Tongji Hospital Median age=62 % male=62%	113 deceased patients (from a cohort of 799 patients, where 274 were included in the study). Of these, 161 patients had recovered and 113 deceased	Laboratory findings (such as white blood cell count, neutrophil, platelet count etc.), abnormalities on chest radiographs, arterial blood gases, complications, primary interventions.	The median age of deceased patients was significantly older than that of recovered patients Male sex was more predominant in patients who died than in those who recovered Chronic hypertension and other cardiovascular comorbidities were more frequent among deceased patients than recovered patients Symptoms related to hypoxemia were more common in deceased patients than in recovered patients Deceased patients more often developed systematic inflammation and multi-organ dysfunction than did recovered patients The indicators of cardiac injury showed more frequent or prominent abnormalities in deceased patients than in recovered patients	**Aim:** To delineate clinical characteristics of patients with covid-19 who died. **Conclusion:** Severe acute respiratory syndrome coronavirus 2 infection can cause both pulmonary and systemic inflammation, leading to multi-organ dysfunction in patients at high risk. Acute respiratory distress syndrome and respiratory failure, sepsis, acute cardiac injury, and heart failure were the most common critical complications during exacerbation of covid-19	Moderate risk of bias
Helms et al 2020 **Design:** Retrospective cohort study with historical control	All patients referred to 4 intensive care units (ICUs) due to covid-19 between March 3rd and 31st 2020 were included Median age=63	**I:** 150 patients with both covid-19 and ARDS were in the covid-19 group and in the matched comparison analysis 77 patients from this group were included	**Primary outcome:** Occurrence of any thrombotic event **Secondary outcome:** Renal replacement therapy (RRT) filter coagulation, the	**Thromboembolic complications (%)** OR: 2.6 (95% CI, 1.1 to 6.1) p=0.035 Most of which was pulmonary embolism. **RRT and lifespan:**	**Aim:** Assess thrombotic risk in severe forms of SARS-CoV-2 infection **Conclusion:** Despite anticoagulation, a high number of patients with	Moderate risk of bias

Setting: Intensive care units in French tertiary hospitals	% male=81.3%	**C:** A historical prospective cohort of "non-covid-19 ARDS" patients (n=233) included between 2014 and 2019 was used for the comparison. In the matched comparison analysis 145 patients from this group were included. The covid-19 and non-covid-19 patients were paired 1:3 on propensity scores based on baseline characteristics that were unbalanced between groups or had clinical relevance as the independent variables (age, sex, medical history of malignancies, cardiovascular diseases, cerebrovascular diseases, venous thrombo-embolic event, immune diseases, chronic liver diseases, chronic renal diseases, respiratory diseases, SAPS II, SOFA, PaO2/ FiO2 on ICU admission, anticoagulant treatment and ECMO)	median lifespan of each RRT circuit, the occurrence of ECMO oxygenator coagulation, hemorrhagic complications and the results of coagulation tests.	The number of RRT circuits per dialyzed patient was higher in covid-19 patients and their median lifespan shorter. **Coagulation parameters:** Prothrombin time, antithrombin, fibrinogen and platelets were significantly higher in covid-19 patients compared to non-covid-19 patients aPTT and D-dimers were significantly lower in covid-19 patients	ARDS and covid-19 develop life-threatening thrombotic complications. The monitoring of anticoagulant treatment should be achieved through anti-Xa measurement, owing to changes of standard hemostasis parameters in this particular pathology. Although Tang et al suggested that anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe covid-19 patients meeting SIC criteria or with markedly elevated D-dimer, higher anticoagulation targets than usual should probably be taken into consideration	

Spiezia et al 2020 **Design:** Nonrandomized prospective case control with matched control group **Setting:** Intesive care unit (ICU) at one hospital in Italy	All consecutive patients admitted to the intensive care unit (ICU) of Padua University Hospital between March 7 and 19, 2020 for acute respiratory distress syndrome (ARDS) due to covid-19	**I:** 22 patients with ARDS due to covid-19 were enrolled in the study. **C:** 44 healthy, age-, sex-, and body weight-matched subjects served as controls for laboratory data.	**Outcomes:** Thromboelasteometry profiles using a ROTEM delta Apparatus. Clotting time, clot formation time (CFT), maximum clot firmness (MCF) and area under the curve (mm 100) Hemoglobin, platelet count, prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, antithrombin, and D-dimer	**ROTEM Profiles:** covid-19 patients had a significantly shorter CFT in INTEM (p=0.000) and EXTEM (p=0.01) covid-19 patients had a significantly higher MCF in INTEM, EXTEM, and FIBTEM (p<0.001 in all comparisons). Fibrinogen and D-dimer plasma levels were significantly higher in covid-19 patients than controls (p<0.000 in both comparisons)	**Aim:** To better characterize covid-19-related coagulation changes **Conclusion:** covid-19 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy. Fibrin formation and polymerization may predispose to thrombosis and correlate with a worse outcome.	Moderate risk of bias
Chen et al 2006 **Design:** Nonrandomized prospective case control with age-matched control group **Setting:** One hospital in Taipei in Taiwan	Patients, family caregivers and health care workers (n=15) who were previously healthy and developed SARS in a cluster outbreak from one index case were enrolled (2–17 May, 2003) Age range: 23 to 45	15 participants who developed SARS from one index case were enrolled in the study. **C:** 15 healthy age-matched adults that had not been exposed to SARS were recruited as control.	**Leukocytes, lymphocytes, neutrophil, monocytes, platelet counts, APTT, PT:** Levels of soluble vascular cell adhesion molecule-1 (sVCAM-1), Levels of plasma soluble Fas ligand (sFasL), intracellular cleaved caspase-3 levels	Patients with SARS had significantly lower lymphocyte (p<0.001) and platelet counts (p<0.001) and significantly higher sVCAM-1 (p=0.003) and sFasL levels (p=0.039(compared to healthy controls. sVCAM-1 levels correlated negatively with total leukocytes (p=0.047) and platelet counts (p=0.031), but positively with plasma sFasL levels (p=0.023) Intracellular cleaved caspase-3 expression was also significantly	**Aim:** To explore the relationship of lymphopenia, thrombocytopenia and clinical manifestations to plasma sFasL and sVCAM-1 levels, as well as intracellular cleaved caspase-3 levels in SARS patients. **Conclusion:** Lymphopenia and thrombocytopenia in SARS patients may be caused, in part, by enhanced vascular sequestration associated with	Moderate risk of bias

				higher in lymphocytes from SARS patients in acute phase than in convalescent stage.	increased sVCAM-1 levels. However, lymphopenia may be due to enhanced cell death. Inhibition of cell adhesion and caspase-3 activation could, therefore, have prevented SARS patients from developing thrombocytopenia and lymphopenia.	

APTT = Activated partial thromboplastin time; **DIC** = Disseminated intravascular coagulation; **FDP** = Fibrin degradation products; **FIB** = Fibrinogen; **PT** = Prothrombin time