

DOES HEPARIN HAVE AN ESSENTIAL ROLE IN THE TREATMENT OF THE COVID-19 PANDEMIC? A REVIEW

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ABSTRACT

Coronavirus 2019 (COVID-19), is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in December 2019. The plasma markers of coagulation, like D-dimers and elevated prothrombin time (PT) are higher in patients with COVID-19. The administration of anticoagulant is beneficial in those patients. Heparins have many therapeutic functions that are important for the controlling of COVID-19-associated clinical manifestations like, neutralization of inflammatory mediators and neutralization of extracellular cytotoxic histones. Many observational studies in different countries have been done and large number of clinical trials have been designed and registered to evaluate efficacy and safety of heparin for patients with COVID-19. The aim of this narrative review is to summarize all available data from previously published studies concerning the use of heparin in treatment of the COVID-19 pandemic.

Keywords: Heparin, COVID-19, D-dimer, Anticoagulant.

Introduction

Coronavirus 2019, is an infectious disease caused by SARS-CoV-2, was first reported in December 2019 (Hippensteel et al., 2020). Since the influenza pandemic of 1918, COVID-19 was the most significant public health crisis all over the world (Hippensteel et al., 2020; Gozzo et al., 2020).

According to large Chinese epidemiological study, 4.7% from symptoms are critical, 13.8% severe and 80.9% mild. The fatality rate is 49% higher in patients with comorbidities like cardiovascular disease, chronic respiratory disease, diabetes mellitus and cancers (Gozzo et al., 2020). The novel coronavirus caused respiratory disease with the symptoms usually affected the respiratory system and required 2 to 14 days to appear (Sheikhi et al., 2020). The degree of symptoms ranged between very mild to very severe and even deaths. Most patients experienced fever, cough, and shortness of breath and many of them are asymptomatic (Kooraki et al., 2020).

The plasma markers of coagulation, such as elevated D-dimers, increased PT and thrombocytopenia are higher in patients with COVID-19 (Van Haren et al., 2020). One of the most important causes of morbidity and mortality in patients with COVID-19 is coagulopathy. The survival is improved after the administration of anticoagulants (Mattioli et al., 2020; Paranjpe et al., 2020). Many studies suggest that the use of unfractionated heparin(UFH) or low molecular weight heparin (LMWH) may improve outcome among patients with COVID-19 (Buijsers et al., 2020).

Heparins have many protective functions in addition to anticoagulant effect that are important for the controlling of clinical manifestations associated with COVID-19 like, neutralization of inflammatory mediators, interfering with leukocyte trafficking and neutralization of extracellular cytotoxic histones (Thachil, 2020). Since heparin has many mechanisms of actions, it is unknown by which mechanism heparin could be beneficial for COVID-19 patients (Gozzo et al., 2020). The aim of this narrative review is to summarize all available data from previously published studies concerning the use of heparin in treatment of the COVID-19 pandemic.

Pathophysiology of COVID-19

Systemic inflammatory response and coagulation system play an important role in the first host defense against pathogens in all types of acute infections including viral ones (Fiusa et al., 2015). The process is multifactorial and complex and involves activation and recruitment of leukocytes through fibrinogen, fibrin and their degradation products to limit microbial dissemination and protect blood vessels (Gozzo et al., 2020). The most important step of SARS-CoV-2 infection is the entry of the virus into host cells which is accomplished by binding of specific virus spike protein to angiotensin-converting enzyme 2 receptor and this process is an important determinant of viral infectivity and pathogenicity (Shang et al., 2020). Post SARS-CoV-2 entry, an immune response is triggered by host factors against the pathogen. This protective mechanism (if uncontrolled) may cause damaging to pulmonary tissues, atrophic changes to lymph nodes and spleen, reduction in lymphocytes in lymphoid organs, in addition to thrombosis, hypercoagulability, and damage to multiple organs (Zabetakis et al., 2020).

The inflammatory changes, especially the (cytokine storm syndrome) are responsible for the hypercoagulable state displayed by many COVID-19 patients (Porfidia & Pola, 2020). The systemic inflammation caused impairment of fibrinolytic systems and pro-coagulant pathways which subsequently resulted in platelet activation and fibrin deposition (Gozzo et al., 2020). The major coagulopathic changes related to COVID-19 include an elevation in serum D-dimer and fibrinogen, reduction in platelets counts, prolongation of both PT and activated partial thromboplastin time (aPTT) (Hippensteel et al., 2020).

Heparin structure and types

Heparin is a preparation of highly sulfated heparan sulfate glycosaminoglycans extracted from the intestine of the porcine (Hippensteel et al., 2020). Since the 1930s, the highly sulfated glycosaminoglycan, heparin, has been employed as an antithrombotic and stays one of the drugs that most commonly prescribed nowadays (Lindahl and Li, 2020).

Heparin is selectively and strongly binds with an enormous number of proteins, the most important one is antithrombin-III (AT3) (an inhibitor of the serine protease) and this interaction is responsible for the anticoagulant activity of heparin (Hippensteel et al., 2020).

Only a part of the polysaccharide chains in heparin preparations have the AT3-binding Penta saccharide structure, and therefore bind AT3 with high affinity and exhibit significant anticoagulant activity (Lindahl *et al.*, 1980).

Hundreds of important protein-interactions with heparin have been explained further than AT3 that has preceded the detection of an enormous number of potential positive and negative effects of heparin of undetermined clinical value (Hippensteel et al., 2020). The molecular weight of LMWH is between 3500–8000 Daltons, in comparison with 15000 Daltons in the UFH. Lower molecular weight heparin molecules inhibit activated coagulation factor X more effectively than they inhibit thrombin (Hull and Pineo, 2000). The use of UFH does have practical topics, mostly concerning the necessity for regular monitoring by aPPT, even though it has been employed for several years. Moreover, the use of UFH is considering problematical (much more than LMWH) (Krishnaswamy et al., 2010).

Regardless of these topics, UFH may still be favored if there is evident renal damage or necessity for reversibility for an urgent intervention (Garcia *et al.*, 2012). Because of its anti-inflammatory effect, LMWH is the most frequently used anticoagulants for the prevention of Venous Thrombo Embolism (VTE). In addition to that LMWH is more favored owing to its familiarity, the comfort of use, and not need laboratory monitoring. Even though, the inquiry of whether the UFH therapeutic doses of LMWH or UFH must be considered for all persons is undetermined at present (Mattioli et al., 2020).

Diagnosis of thrombosis in patients with COVID-19

At present, very little is recognized on the exact occurrence of VTE among hospitalized patients with COVID-19 pneumonia, since the diagnostic tests cannot be simply done in those patients, another causes are deficiency of suitable protective individual equipment or patients are too unstable (Porfidia & Pola, 2020). Coagulation abnormalities are gradually identified in hospitalized patients with COVID-19, involving rising PT, elevated D-dimer, and raised fibrinogen. Even though, an increased D-dimer concentration is the most characteristic finding in patients with COVID-19 and a prothrombotic state (Berger et al., 2020) D-dimer is a degradation product of cross-linked fibrin and is a sign of blood clot formation and its consequent fibrinolysis (Oudkerk et al., 2020).

Several studies in patients with COVID-19 have regularly revealed a very strong relationship between increased the levels of D-dimer and poor prognosis and/ or severe disease (Tang et al., 2020). For asymptomatic deep vein thrombosis, screening ultrasound is not normally done in seriously ill patients. However, for seriously ill patients with a clinical suspicion for VTE, lower extremity ultrasound is recommended. In general, screening ultrasound is associated with increased danger of employees exposure and resource utilization during the COVID-19 pandemic (Moore et al., 2020).

Rationale use of heparin in COVID-19

Heparin has many beneficial mechanisms of action in patients with COVID-19 away from anticoagulation (Buijsers et al., 2020). Heparin has antiviral activity accomplished by binding the spike protein of the SARS-CoV-2 and thus functioning as viral entry competitive inhibitor (Kim et al., 2020). Interestingly, LMWH did not bind the spike protein of the virus, and due to the lack of this competitive mechanism it may be less possible to have direct antiviral activity (Hippensteel et al., 2020). The anti-inflammatory effect of heparin may be explained by its binding and modulating proteins such as cytotoxic peptides, chemokines, growth factors, cytokines, tissue destructive enzymes, adhesion molecules, and other proteins that involved in inflammation (Gozzo et al., 2020). Heparin has anti-coagulant effect (which is the most important action) mediated by several mechanisms, including catalyzing the action of AT3, promoting tissue factor pathway inhibitor expression, endothelium releasing of tissue plasminogen activator, decreasing the expression of tissue factor, and through the release of tissue plasminogen activator by the endothelium (Van Haren et al., 2020).

Methods

In this study a number of previously published studies in different countries were collected and summarized since the incidence of COVID-19 till December 2020. Studies involved anticoagulant interventions other than heparin were excluded. The included participants were patients infected with COVID-19 from both sexes. Some of these studies used UFH, the other used LMWH. Also some of them used standard prophylactic doses while the other used higher therapeutic doses, as shown in Table (1)

Table 1: summarized characteristics of included studies

Authors	Country	Drug	Number of participants	Gender	Age	Study design	Objectives of study	Outcomes of study	Comments
(Takayama et al., 2020)	Japan	UFH	47 26 in therapeutic dose 21 in prophylactic dose	45 males 2 females	Median 57 years	Retrospective historical control study	1. Comparison of in-hospital mortality between two groups. 2. To evaluate the anticoagulants adverse events.	Unfractionated heparin at therapeutic doses is better than prophylactic doses for severe COVID-19 patients.	1. This is a preprint study, which is not subjected to peer review 2. The sample size of this study is limited.
(Ayerbe et al., 2020)	Spain	UFH	2075 persons 1734 received heparin 285 did not	1256 males 819 females	Mean 67.57 years	Observational	To assess the mortality rate in patients who treated with heparin and patients who did not.	The higher mortality rate was seen in patients who did not receive heparin	The results of this study can be generalized due to the large sample size and multicenter.
(Stabile et al., 2020)	Italy	LMWH	257 patients 131 received prophylactic dose 126 received therapeutic dose	174 males 83 females	Mean 69.3 years	Retrospective cohort study	To assess in-hospital mortality between patients treated with prophylactic doses versus therapeutic doses	Mortality was significantly higher in patients treated with prophylactic doses	There is a potential selection bias and residual confounding in this study
(Stessel et al., 2020)	Belgium	LMWH	72 Patients 46 received pr-ophylactic dose of LMWH, the other received more aggressive doses	49 males 23 females	Median 69.5 years in prophylactic dose group Median 62 years in aggressive	A longitudinal controlled before-after study	To assess one-month mortality between two groups	One-month mortality was lower in the patients receiving the more aggressive thromboprophylactic doses	1. Unidentified confounders due to quasi-experimental study design 2. The results of this study cannot be generalized due to monocentric.

					e dose group				
(Mattioli et al., 2020)	Italy	LMWH	105 patients treated with subcutaneous enoxaparin	61 males 44 females	Mean 73.7 years	Retrospective cohort study	To determine the safety of intermediate dose of LMWH	Low rate of adverse events was detected in patients who received intermediate doses of LMWH	There is a selection bias as a result of monocentric, limited sample size and there is no control group received standard therapy.
(Pesavento et al., 2020)	Italy	LMWH UFH	324 patients 240 received sub-therapeutic doses and 84 received higher doses of anti-coagulants.	181 males, 143 females	Median 71 years	Retrospective	To assess the incidence of bleeding between two groups.	The rate of bleeding events was high in patients treated with sub-therapeutic doses.	There is no standardized approach for the detection of VTE disorders

Heparin possible adverse and off-target effects

The entire heparins adverse effects are connected to the extensive biological activities diversity, and the most critical safety matter is bleeding that be caused by the heparin potency as an anticoagulant (Alban, 2012). There is a 10–15% risk of substantial bleeding when heparin use as a therapeutic anticoagulant (Hippensteel, 2020). Although the occurrence of bleeding is difficult to define, many factors may increase the risk. However, patients with renal failure, in addition to the elderly are usually individual baseline bleeding indicators in all patients taking antithrombotic therapy (Middeldorp et al., 2020).

Moreover, pulmonary embolism, malignancy, surgery, recent bleeding or trauma, long hospital stay, raised cardiac biomarkers, and anemia are similarly related to the bleeding induced by heparin (Lodigiani et al., 2020). Another complication of heparin therapy is Heparin-Induced Thrombocytopenia that is expected to occur in 0.2–3% of patients receiving heparin. This severe adverse effect is determined by the antibodies formation that is specific to the protein platelet factor IV which results in the inconsistent development of thrombosis and life-threatening thrombocytopenia (Hippensteel, 2020). The correlation between osteoporosis and heparin therapy has been suspected for many years. Both LMWH and UFH make a dose-dependent decrease in cancellous bone volume by reducing bone formation. However, only UFH was established to enhance bone resorption as indicated by many studies (Signorelli et al., 2019).

The incidence of heparin-induced osteoporosis seemed to be closely associated with the dosage (15000 U or more daily), and the duration of treatment (more than 4–5 months), but the pathogenesis is inadequately comprehended (Gennari et al., 1998). Lastly, heparin may have various other unknown effects resulting from its heterogeneous structure. Moreover, UFH is made up of a mix of distinctive biologically derived heparan sulfate polysaccharides, that exhibits a wide diversity of sulfation sequences, besides containing a Penta saccharide sequence involved in the activation of the AT3 (consequently anticoagulation). As a result, the non-anticoagulant sulfation sequences enable heparin to bind to many growth factors and possibly causing organ-harmful and organ-protecting influences (Hippensteel et al., 2020).

The use of heparin during pregnancy

Many risk factors cause thrombosis in pregnant women like thrombophilia, obesity, and prolonged immobilization (Koyuncu et al., 2020). Additionally, there is increased risk of thrombosis in pregnant women infected with COVID-19 and the recommendations for thromboprophylaxis have been proposed by many international organizations for both pregnant and postpartum women infected with COVID-19 (D'Souza et al., 2020). However, how COVID-19 infection caused a thromboembolic complication in pregnant woman and whether it is an indication for thromboprophylaxis is still unknown (Koyuncu et al., 2020).

on-going clinical trials about heparin:

More than 3500 studies have been designed and registered to evaluate efficacy and safety of interventions for patients with COVID-19 (Tritschler et al., 2020). Among these interventions is evaluating the effect of LMWH or UFH in hospitalized patients infected with COVID-19 using different dosing regimens of anticoagulants as recommended by the World Health Organization guidelines (Gozzo et al., 2020; Tritschler et al., 2020). The main outcome measures of these trials are hard endpoints like survival or mortality (Gozzo et al., 2020).

A brief description of some of these trials:

Cohort (CORIMMUNO-COAG)

In this protocol the safety and efficacy of Tinzaparin or unfractionated heparin will be evaluated in COVID-19 patients (808 participants) using randomized open-label clinical trial where the patients will be randomly allocated to therapeutic anticoagulation group versus standard of care group using prophylactic doses of heparin (Tritschler et al., 2020).

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A multinational randomized open-label clinical trial will be done to compare the treatment with nebulized UFH plus standard care to standard care alone, and whether this combination will reduce the duration of mechanical ventilation in patients with COVID-19, 1800 patients will participate in the overall study (Van Haren et al., 2020).

Conclusion

Coronavirus may affect many systems in the body other than the respiratory system like the coagulation system which is shifted toward the pro-coagulant state. Heparin has a potential role in the treatment of the COVID-19 since it has anticoagulant, ant inflammatory and antiviral activities, also the administration of heparin is associated with improved survival in those patients. In general, there are no significant differences between UFH and LMWH in the treatment of thrombosis. However, using the therapeutic doses shows advantages over the prophylactic doses both in reducing mortality and in decreasing the incidence of side effects. At the time of writing, many registered randomized controlled clinical trials in different countries are currently undertaken to evaluate the optimum doses and safety of UFH or LMWH used in patients with COVID-19.

Recommendations for further studies

Randomized clinical trials about heparin use in COVID-19 are immediately required, although there are various well-designed ongoing clinical trials awaiting completion. More information will be obtained in the future after the appropriate drug for treating COVID-19 is found among the candidate drugs, with knowledge of the benefits and risks of these drugs.

Conflicts of Interest:

The authors declare no conflicts of interest.

References

- Alban S. (2012). Adverse effects of heparin. *Handbook of experimental pharmacology*, (207), 211–263. https://doi.org/10.1007/978-3-642-23056-1_10
- Ayerbe, L., Risco, C., & Ayis, S. (2020). The association between treatment with heparin and survival in patients with Covid-19. *Journal of thrombosis and thrombolysis*, 50(2), 298–301. <https://doi.org/10.1007/s11239-020-02162-z>
- Berger, J. S., Kunichoff, D., Adhikari, S., Ahuja, T., Amoroso, N., Aphinyanaphongs, Y., Cao, M., Goldenberg, R., Hindenburg, A., Horowitz, J., Parnia, S., Petrilli, C., Reynolds, H., Simon, E., Slater, J., Yaghi, S., Yuriditsky, E., Hochman, J., & Horwitz, L. I. (2020). Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients with COVID-19. *Arteriosclerosis, Thrombosis, and Vascular Biology*, October 2539–2547. <https://doi.org/10.1161/ATVBAHA.120.314872>
- Buijssers, B., Yanginlar, C., Maciej-Hulme, M. L., de Mast, Q., & van der Vlag, J. (2020). Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine*, 59, 102969. <https://doi.org/10.1016/j.ebiom.2020.102969>
- D'Souza, R., Malhamé, I., Teshler, L., Acharya, G., Hunt, B. J., & McLintock, C. (2020). A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19. *Acta Obstetrica et Gynecologica Scandinavica*, 99(9), 1110–1120. <https://doi.org/10.1111/aogs.13962>
- Fiusa, M. M. L., Carvalho-Filho, M. A., Annichino-Bizzacchi, J. M., & De Paula, E. V. (2015). Causes and consequences of coagulation activation in sepsis: An evolutionary medicine perspective. *BMC Medicine*, 13(1), 1–9. <https://doi.org/10.1186/s12916-015-0327-2>
- Garcia, D. A. *et al.* (2012) 'Parenteral anticoagulants - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines', *Chest*, 141(2 SUPPL.), pp. e24S-e43S. doi: 10.1378/chest.11-2291.
- Gennari, C., Martini, G., & Nuti, R. (1998). Secondary osteoporosis. *Aging Clinical and Experimental Research*, 10(3), 214–224.
- Gozzo, L., Viale, P., Longo, L., Vitale, D. C., & Drago, F. (2020). The Potential Role of Heparin in Patients With COVID-19: Beyond the Anticoagulant Effect. A Review. *Frontiers in Pharmacology*, 11, 1307. <https://doi.org/10.3389/fphar.2020.01307>
- Hippensteel, J. A., LaRiviere, W. B., Colbert, J. F., Langou t-Astri, C. J., & Schmidt, E. P. (2020). Heparin as a therapy for COVID-19: Current evidence and future possibilities. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, 319(2), L211–L217. <https://doi.org/10.1152/AJPLUNG.00199.2020>
- Hull, R. D. and Pineo, G. F. (2000) 'Low-molecular-weight heparin in the treatment of venous thromboembolism', *Seminars in Thrombosis and Hemostasis*, 26(3 SUPPL. 1), pp. 61–67. doi: 10.1055/s-2000-9495.
- Kim, S. Y., Jin, W., Sood, A., Montgomery, D. W., Grant, O. C., Fuster, M. M., Fu, L., Dordick, J. S., Woods, R. J., Zhang, F., & Linhardt, R. J. (2020). Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. *Antiviral Research*, 181. <https://doi.org/10.1016/j.antiviral.2020.104873>
- Kooraki, S., Hosseiny, M., Myers, L., & Gholamrezanezhad, A. (2020). Coronavirus (COVID-19) Outbreak : What the Department of Radiology Should Know. *Journal of the American College of Radiology*, 17(4), 447–451. <https://doi.org/10.1016/j.jacr.2020.02.008>

- Koyuncu, K., Sakin, Ö., Aktaş, H. A., Şahin, K., Aygün, T., Anğın, A. D., & Kale, A. (2020). Thromboprophylaxis in Covid-19 Positive Pregnant Women. *Southern Clinics of Istanbul Eurasia*, 31(3).
- Krishnaswamy, A., Lincoff, A.M., Cannon, C.P. (2010). The use and limitations of unfractionated heparin. *Crit Pathw Cardiol*, 9(1):35-40.
- Lindahl, U., Bäckström, G., Thunberg, L., & Leder, I. G. (1980). Evidence for a 3-O-sulfated D-glucosamine residue in the antithrombin-binding sequence of heparin. *Proceedings of the National Academy of Sciences of the United States of America*, 77(11), 6551–6555. <https://doi.org/10.1073/pnas.77.11.6551>
- Lindahl, U. and Li, J. P. (2020) 'Heparin – An old drug with multiple potential targets in Covid-19 therapy', *Journal of Thrombosis and Haemostasis*, 18(9), pp. 2422–2424. doi: 10.1111/jth.14898.
- Lodigiani, C., Iapichino, G., Carenzo, L., Cecconi, M., Ferrazzi, P., Sebastian, T., Kucher, N., Studt, J. D., Sacco, C., Bertuzzi, A., Sandri, M. T., Barco, S., & Humanitas COVID-19 Task Force (2020). Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thrombosis research*, 191, 9–14. <https://doi.org/10.1016/j.thromres.2020.04.024>
- Mattioli, M., Benfaremo, D., Mancini, M., Mucci, L., Mainquà, P., Polenta, A., Baldini, P. M., Fulgenzi, F., Dennetta, D., Bedetta, S., Gasperoni, L., Caraffa, A., & Frausini, G. (2020). Safety of intermediate dose of low molecular weight heparin in COVID-19 patients. *Journal of thrombosis and thrombolysis*, 1–7. Advance online publication. <https://doi.org/10.1007/s11239-020-02243-z>.
- Middeldorp, S., Coppens, M., van Haaps, T. F., Foppen, M., Vlaar, A. P., Müller, M. C. A., Bouman, C. C. S., Beenen, L. F. M., Kootte, R. S., Heijmans, J., Smits, L. P., Bonta, P. I., & van Es, N. (2020). Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of Thrombosis and Haemostasis*, 18(8), 1995–2002. <https://doi.org/10.1111/jth.14888>
- Moores, L. K., Tritschler, T., Brosnahan, S., Carrier, M., Collen, J. F., Doerschug, K., Holley, A. B., Jimenez, D., Le Gal, G., & Rali, P. (2020). Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. *Chest*, 158(3), 1143–1163.
- Oudkerk, M., Buller, H. R., Kuijpers, D., van Es, N., Oudkerk, S. F., McLoud, T., Gommers, D., van Dissel, J., ten Cate, H., & van Beek, E. J. R. (2020). Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: Report of the national institute for public health of the Netherlands. *Radiology*, 297(1), E216–E222. <https://doi.org/10.1148/radiol.2020201629>
- Paranjpe, I., Fuster, V., Lala, A., Russak, A. J., Glicksberg, B. S., Levin, M. A., Charney, A. W., Narula, J., Fayad, Z. A., Bagiella, E., Zhao, S., & Nadkarni, G. N. (2020). Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. *Journal of the American College of Cardiology*, 76(1), 122–124. <https://doi.org/10.1016/j.jacc.2020.05.001>
- Pesavento, R., Ceccato, D., Pasquetto, G., Monticelli, J., Leone, L., Frigo, A., Gorgi, D., Postal, A., Marchese, G. M., Cipriani, A., Saller, A., Sarais, C., Criveller, P., Gemelli, M., Capone, F., Fioretto, P., Pagano, C., Rossato, M., Avogaro, A., ... Vettor, R. (2020). The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. *Journal of Thrombosis and Haemostasis*, 18(10), 2629–2635. <https://doi.org/10.1111/jth.15022>
- Porfidia, A., & Pola, R. (2020). Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies and the lack of guidelines. *Journal of Thrombosis and Thrombolysis*, 50(1), 68–71. <https://doi.org/10.1007/s11239-020-02125-4>
- Shang, J., Wan, Y., Luo, C., Ye, G., Geng, Q., Auerbach, A., & Li, F. (2020). Cell entry mechanisms of SARS-CoV-2. *Proceedings of the National Academy of Sciences of the United States of America*, 117(21), 11727–11734. <https://doi.org/10.1073/pnas.2003138117>
- Sheikhi, K., Shirzadfar, H., & Sheikhi, M. (2020). A Review on Novel Coronavirus (Covid-19): Symptoms , Transmission and Diagnosis Tests. *Research in Infectious Diseases and Tropical Medicine*, 2(1), 1–8. <https://doi.org/10.33702/ridtm.2020.2.1.1>

- Signorelli, S. S., Scuto, S., Marino, E., Giusti, M., Xourafa, A., & Gaudio, A. (2019). Anticoagulants and Osteoporosis. *International journal of molecular sciences*, 20(21), 5275. <https://doi.org/10.3390/ijms20215275>.
- Stabile, M., Aschieri, D., & Franco, C. (2020). Covid-19 and low molecular weight heparin therapy: retrospective study of 257 patients. 1–11.
- Stessel, B., Vanvuchelen, C., Bruckers, L., Geebelen, L., Callebaut, I., Vandenbrande, J., Pellens, B., Van Tornout, M., Ory, J. P., van Halem, K., Messiaen, P., Herbots, L., Ramaekers, D., & Dubois, J. (2020). Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. *Thrombosis Research*, 194(July), 209–215. <https://doi.org/10.1016/j.thromres.2020.07.038>.
- Takayama W., Endo A., Otomo Y., (2020). Anticoagulation Therapy Using Unfractionated Heparin at a Therapeutic Dose for Coronavirus Disease 2019 Patients With Severe Pneumonia: A Retrospective Historical Control Study, 29 October 2020, PREPRINT (Version 1) available at Research Square [<https://doi.org/10.21203/rs.3.rs-97391/v1>].
- Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*, 18(4), 844–847. <https://doi.org/10.1111/jth.14768>
- Thachil J. (2020). The versatile heparin in COVID-19. *Journal of thrombosis and haemostasis : JTH*, 18(5), 1020–1022. <https://doi.org/10.1111/jth.14821>
- Tritschler, T., Mathieu, M. E., Skeith, L., Rodger, M., Middeldorp, S., Brighton, T., Sandset, P. M., Kahn, S. R., Angus, D. C., Blondon, M., Bonten, M. J., Cattaneo, M., Cushman, M., Derde, L., DeSancho, M. T., Diehl, J. L., Goligher, E., Jilma, B., Jüni, P., Lawler, P. R., (2020). Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. *Journal of thrombosis and haemostasis : JTH*, 18(11), 2958–2967. <https://doi.org/10.1111/jth.15094>.
- Van Haren, F. M. P., Page, C., Laffey, J. G., Artigas, A., Camprubi-Rimblas, M., Nunes, Q., Smith, R., Shute, J., Carroll, M., Tree, J., Carroll, M., Singh, D., Wilkinson, T., & Dixon, B. (2020). Nebulised heparin as a treatment for COVID-19: Scientific rationale and a call for randomised evidence. *Critical Care*, 24(1), 1–11. <https://doi.org/10.1186/s13054-020-03148-2>.
- Zabetakis, I., Lordan, R., Norton, C., & Tsoupras, A. (2020). Covid-19: The inflammation link and the role of nutrition in potential mitigation. *Nutrients*, 12(5), 1466. <https://doi.org/10.3390/nu12051466>