Thesis

Pathophysiologic and clinical aspects of Covid-19-related vasculopathy

submitted by

Thiemo Greistorfer

in partial fulfillment of the requirements for the degree of

Doktor(in) der gesamten Heilkunde

(Dr.(in) med. univ.)

at the

Medical University of Graz

executed at the

University department of Angiology

under the supervision of

Franz Hafner, M.D., Priv.Doz.

Philipp Jud, M.D.

Graz, 12.11.2022

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 12.11.2022 Thiemo Greistorfer m.p.

Acknowledgements

Firstly, I would like to thank my supervisors DDr. Philipp Jud and Priv.-Doz. Dr. Franz Hafner for their great support and advice throughout the literature research and writing process of this diploma thesis.

I would also like to thank my parents and my entire family for their continual support and encouragement, who greatly contributed to my university studies, as well as my friends for their never-ending friendship.

Finally, a special and deep gratitude belongs to my always supportive girlfriend Katharina, who kept on endorsing me through my whole university studies and everything beyond this. I wish to thank her for her confidence and patience during my studies and the writing process of this thesis.

Table of contents

List of Abbreviations

+ssRNA: positive single-stranded RNA

AAV: ANCA-associated vasculitides

ACE-2: angiotensin-converting-enzyme 2

ACS: acute coronary syndrome

ADAMTS13:Ac: ADAMTS13 activities

ALI: Acute limb ischemia

ANCA: antineutrophil cytoplasmic antibodies

Ang 1-7: angiotensin 1-7

Ang: angiotensin

ARDS: acute respiratory distress syndrome

ATE: arterial thromboembolisms

BMI: body mass index

CDC: Centers for Disease Control and Prevention

cfDNA: cell-free deoxyribonucleic acid

CHCC: International Chapel Hill Consensus Conference

citH3: citrullinated histone H3

CLIA: chemiluminescent immunoassays

CMV: cytomegalovirus

CNS: central nervous system (CNS)

COVID-19: coronavirus disease 2019

CRP: C-reactive protein

CSF: cerebrospinal fluid

CT: computed tomography

CTA: CT angiography

cTn: cardiac troponins

CV: cryoglobulinemic vasculitis

CVT: Cerebral venous thrombosis

DAPT: dual antiplatelet therapy

DIC: disseminated intravascular coagulation

DNA-MPO: deoxyribonucleic acid myeloperoxidase

DOACs: direct oral anticoagulants

DVT: deep vein thrombosis

EBV: Epstein-Barr virus

ECG: electrocardiogram

EF: ejection fraction

EGPA: eosinophilic granulomatosis with polyangiitis

ELISA: enzyme-linked immunosorbent assays

EM: electron microscopy

ESR: erythrocyte sedimentation rate

ESVS: European Society for Vascular Surgery

FiO_2: fraction of inspired oxygen

FXII: factor XII

GCA: giant cell arteritis

GPA: granulomatosis with polyangiitis

HBV: hepatitis B virus

HCV: hepatitis C virus

HIV: human immunodeficiency virus

HLA: human leukocyte antigen

IA: Infectious aortitis

IC: immune complex

ICU: intensive care unit

IHD: Ischemic heart disease

IL: interleukin

INR: international normalized ratio

KD: Kawasaki disease

LDH: lactate dehydrogenase

LDL: low-density lipoprotein

LFIA: lateral flow immunoassays

LMWH: low molecular weight heparin

MASR: MAS receptor

MC: mixed cryoglobulinemia

MERS: Middle East respiratory syndrome

MI: Myocardial infarction

MIS-C: Multisystem Inflammatory Syndrome – in children

MPA: microscopic polyangiitis

MRI: magnetic resonance imaging

NAATs: nucleic acid amplification tests

NETs: neutrophil extracellular traps

NIH: National Institute of Health

NIHSS: National Institute of Health Stroke Scale

NSAIDs: nonsteroidal anti-inflammatory drugs

NSTE-ACS: non-ST-segment elevation-acute coronary syndrome

NT-proBNP: NT-pro-brain natriuretic peptide

PAD: peripheral arterial disease

PAI-1: plasminogen activator inhibitor 1

PAN: polyarteritis nodosa

PaO_2: arterial blood oxygen tension

PaO_2/FiO_2: oxygenation index

PARs: protease-activated receptors

PCI: percutaneous coronary intervention

PE: pulmonary embolism

PESI: pulmonary embolism severity index

PIMS-TS: Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection

PT: prothrombin time

RAS: renin-angiotensin system

RdRp: RNA-dependent RNA-polymerase

RF: rheumatoid factor

RT-PCR: reverse-transcriptase polymerase chain reaction

rtPA: recombinant tissue plasminogen activator

SARS-CoV-2: severe acute respiratory syndrome-coronavirus 2

SARS: severe acute respiratory syndrome

sCD40L: soluble CD40-ligand

SMC: smooth muscle cell

$SPpO_2$: oxygen saturation

STEMI: ST-segment myocardial infarction

sTM: soluble thrombomodulin

SVT: superficial vein thrombosis

TAK: Takayasu´s arteritis

TAT: thrombin-antithrombin complex

TF: tissue factor

TIA: transient ischemic attack

TMPRSS2: transmembrane protease serine subtype 2

TNF: tumor necrosis factor

TTP: thrombotic thrombocytopenic purpura

UFH: Unfractionated heparin

VOC: Variants of Concern

VOI: Variants of Interest

VTE: venous thromboembolism

vWF: von Willebrand factor

vWF:Ag: vWF antigen

VZV: varizella zoster virus

WBC: white blood cell

WHO: World Health Organization

1 Zusammenfassung

Die aktuelle Covid-19-Pandemie, ausgelöst durch das Ende 2019 aufgekommene Coronavirus SARS-CoV-2, hat zu einem enormen Erkenntnisgewinn auf dem Gebiet der Infekt-assoziierten Vaskulopathien geführt. Ein komplexes Zusammenspiel zwischen Endothel, Immunzellen und Gerinnung scheint diese vaskulären Ereignisse auszulösen. Insbesondere Patientinnen und Patienten mit schweren Covid-19 Verläufen entwickeln häufig arterielle und venöse Thromboembolien. Zusätzlich wurden spezielle Vaskulitiden in der Literatur beschrieben. Ziel dieser Übersichtsarbeit war es, die wichtigsten pathophysiologischen und klinischen Aspekte Covid-19-assoziierter Vaskulopathien hinsichtlich ihrer Entstehung im Gefäßsystem und der beteiligten Mechanismen zu bewerten. Folglich wurde ein Hauptaugenmerk auf die klinischen Aspekte der Vaskulopathien gelegt, inklusive ihrer Epidemiologie, klinischen Merkmalen, Management und Behandlung, sowie Vergleiche mit Nicht-Covid-19-Kohorten gezogen.

Eine elektronische Suche wurde zwischen Februar 2021 bis September 2022 in den folgenden Datenbanken durchgeführt: MEDLINE, Cochrane Library Database, Google scholar und ClinicalTrials.gov. Die einbezogenen Artikelarten reichten von Laborstudien und Fallserien, über Beobachtungsstudien und Kohortenstudien, bis zu kontrollierten klinischen Studien und Metaanalysen.

Die pathophysiologischen Aspekte zeigten die zentrale Interaktion zwischen virusbedingter endothelialer Dysfunktion, NET-Bildung und Immunthrombose bei der Bildung von Mikrothromben über das gesamte Gefäßsystem hinweg. Es konnte gezeigt werden, dass verschiedene Biomarker, darunter D-Dimer, von Willebrand Factor (vWF)-Antigen, lösliches Thrombomodulin, Plasminogen-Aktivator-Inhibitor 1 (PAI-1) und die ADAMTS13-Aktivität auf die auslösenden Mechanismen hinweisen und zudem von prognostischem Wert sind. Venöse thromboembolische Ereignisse und Schlaganfälle werden bei Patientinnen und Patienten mit Covid-19 im Vergleich zu Nicht-Covid-19-Patientinnen und Patienten häufiger beobachtet, während die klinischen Merkmale trotz einer Tendenz zu schwereren Verläufen nur geringfügige Unterschiede aufweisen. Darüber hinaus war die Sterblichkeitsrate bei Patientinnen und Patienten mit gleichzeitiger Covid-19-Infektion und Lungenembolie erhöht, was auch für die meisten arteriellen thrombotischen Komplikationen galt. Während Endotheliitis ein häufiger Befund bei Covid-19 ist,

sind echte Vaskulitiden im Zusammenhang mit SARS-CoV-2 selten und treten vorwiegend in Form einer kutanen Vaskulitis der kleinen Gefäße oder der Kawasaki-ähnlichen Erkrankung auf, die typischerweise mit dem Multisystem-Entzündungssyndrom assoziiert ist.

Diese Übersichtsarbeit zeigt somit, dass thrombotische Ereignisse bei hospitalisierten Covid-19-Patientinnen und Patienten häufig sind und durch eine Kaskade von Mechanismen entstehen, die durch verschiedene Biomarker detektiert werden können. Während Symptomatik, Management und Behandlungsansätze großteils denen von Nicht-Covid-19-Fällen ähneln, weisen hospitalisierte Covid-19-Patientinnen und Patienten häufig gesteigerte Inzidenzen und Mortalitätsraten auf.

2 Abstract

The current Covid-19 pandemic, caused by the emerged coronavirus SARS-CoV-2 in late 2019, leads to a tremendous knowledge gain in the field of infection-associated vasculopathies. A complex interaction between the endothelium, immune cells and coagulation seems to trigger these vascular events. Especially, patients with severe Covid-19 develop frequently arterial and venous thrombotic events, and certain vasculitides have also been described in the literature. The aim of this review was to assess the key pathophysiologic and clinical aspects of Covid-19 associated vasculopathies regarding their occurence within the vasculature and the involved mechanisms. Clinical aspects of vasculopathies were reviewed with special emphasis on their epidemiology, clinical features, management and treatment and comparison to non-Covid-19 cohorts.

An electronic search was conducted from February 2021 to September 2022 in the following databases: MEDLINE, the Cochrane Library Database, Google scholar, and ClinicalTrials.gov. The received and included article types ranged from laboratory studies and case series, over observational studies and cohort studies to controlled clinical trials and meta-analyses.

Pathophysiologic aspects revealed crucial interactions between virus-triggered endothelial dysfunction, NET formation and immunothrombosis in the formation of microthrombi throughout the vasculature. Different biomarkers, including D-dimer, von Willebrand factor (vWF) antigen, soluble thrombomodulin (sTM), plasminogen activator inhibitor 1 (PAI-1), and ADAMTS13-activities were found to indicate the exaggerating mechanisms and are also of prognostic value. Venous thromboembolic events and strokes are more frequently observed in patients with Covid-19 compared to non-Covid-19 patients, while clinical features only showed minor differences despite trends towards more severe courses. Additionally, mortality rates were increased in patients with concomitant Covid-19 and pulmonary embolism (PE), which also applied to most arterial thrombotic complications. While endotheliitis is a common finding in Covid-19, genuine vasculitides related to SARS-CoV-2 are rare findings and predominantly occur as cutaneous small vessel vasculitis and Kawasaki-like disease, typically associated with multisystem inflammatory syndrome.

This review indicates that thrombotic events in hospitalized Covid-19 patients are common and arise through a cascade of mechanisms, which can be detected using

different biomarkers. While the symptomatology, management and treatment approaches mostly resemble those of non-Covid-19 cases, epidemiology and mortality rates are often increased in hospitalized Covid-19 patients.

3 Introduction

The current Covid-19 pandemic fundamentally changed everyday life worldwide and strained health care systems in an unparalleled manner. Today, humankind arranged with the constant presence of Covid-19, but the painful experiences with millions of deaths, especially during the first months of the pandemic, should not be forgotten. The comprehensive effects of Covid-19 also affect the vascular system and vasculopathies, including arterial and venous thromboembolic events and vasculitides, are commonly described in hospitalized patients. Several studies obtained data on the pathophysiological and clinical aspects of vasculopathies in Covid-19, but comprehensive reviews combining their emergence and clinical features are scarce. Moreover, the comparison of Covid-19 associated vasculopathies with cases from a pre-pandemic era could support the discovery of specific characteristics and thereby influence the further management and treatment approach in affected patients. Thus, the upcoming review provides data on the most significant aspects of Covid-19 associated vasculopathies with a focus on their pathophysiology and comparison of the major entities to non-Covid-19 cohorts.

3.1 Severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 belongs to the family of coronaviridae and genome sequencing combined with phylogenic analysis classified this novel coronavirus as a betacoronavirus. As a coronavirus, SARS-CoV-2 is an enveloped single-stranded positive RNA (+ssRNA) virus. (1, 2) The typical crown-like appearance in electron micrographs leads to the name of this virus family. Their membrane is riddled with glycoprotein spikes, encompassing the nucleocapsid with the viral genome. The size of the RNA genome of coronaviruses varies between 27 and 32 kb, making them the largest known RNA viruses. The genome encodes for proteins, which are important for RNA replication and the four structural proteins S (spike), E (envelope), M (membrane) and N (nucleocapsid). While the S-, E- and M-proteins build the viral envelope, the N-protein connects with the genome forming the nucleocapsid. (3, 4) Other representatives of the same genus include the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronaviruses.

Coronaviruses are well known pathogens, having the ability to infect different species and typically causing respiratory diseases in humans. (1, 2) To enlighten the viral transmission from animals to humans, it is of great interest to discover the origins of the virus in the animal kingdom. The approach is based on genome sequencing of different betacoronaviruses in animals to identify the direct ancestors of the SARS-CoV-2, which potentially spilled over to humans. Analyses revealed a certain bat coronavirus in the bat species *Rhinolophus affinis* to share the highest average genetic similarity with SARS-CoV-2 known so far. The virus named RaTG13 matches with the reference sequence of SARS-CoV-2 to the extent of 96.2%. (1) Three additional bat viruses, namely RmYN02, RpYN06, and PrC31, are, however, closer related in most of the virus genome, hence sharing a more recent common ancestor. (5) This and other findings support the hypothesis that bat coronaviruses are the likely precursors of SARS-CoV-2, and thus bats could serve as the natural reservoir. (1) Another species of interest are pangolins, in which many SARS-CoV-2 related viruses where discovered. In comparison to asymptomatic bats, pangolins developed symptoms after infection suggesting that they probably act as an intermediate host, rather than the pathogen reservoir. The role of alternate hosts is well known from previous spillovers of bat coronaviruses, ultimately passing the diseases to humans. The above-mentioned MERS and SARS coronaviruses were both transmitted to humans via this indirect route. But in their cases, the viral genomes in the intermediate hosts were almost identical to that in humans, while the closest related strain to SARS-CoV-2 in pangolins up to date only reaches 92% conformity. (1) This is in line with the world health organization (WHO) report on the origins of SARS-CoV-2 from March 2021, which was also not able to detect this probable intermediary host, linking the ancestral progenitor bat coronavirus with the novel human betacoronavirus. Consequently, the direct precursor virus as well as the assumed “missing link” remain unknown. Further studies might enlighten the origin and spillover of SARS-CoV-2. With the prevailing knowledge, this pathway of emergence occurs as the most likely, followed by direct zoonotic transmission, introduction by the cold/food chain, and the outbreak due to a laboratory incident, as a highly unlikely event. (5, 6)

3.1.1 SARS-CoV-2 Variants

Since the transmission of SARS-CoV-2 among humans, the virus continuously evolves over time gathering mutations, which give rise to different variants. These mutations influence the characteristics of the variants concerning e.g. the virulence, transmissibility and immunogenicity. (2, 4) To classify arising variants, different scientific and community nomenclatures were introduced. One familiar scientific nomenclature is the Pango lineage, which names the variants like B.1.1.7. In May 2021, the WHO announced a new nomenclature system based on the Greek alphabet with the intention to simplify conversations about variants in the public in addition to the established scientific systems.

One of the highlighted mutations recognized early during the pandemic was the spike protein amino acid change D614G (replacement of aspartic acid by glycine). Variants bearing this polymorphism were associated with a higher viral load in the upper respiratory tract of infected patients and significantly elevated infectious titers compared to the D614 variant in vitro. (7) Nowadays, the vast majority of circulating SARS-CoV-2 lineages bear this spike protein polymorphism including all current variants of concern. (2)

The WHO classifies selected variants as either Variants of Interest (VOI) or Variants of Concern (VOC). VOI include variants with assumed or established phenotypic changes due to mutations in comparison with reference strains. Additionally, VOI feature one of the following characteristics: proven community contagions, multiple Covid-19 cases, detected in various countries or otherwise identified as a VOI from the WHO. VOC meet the criteria of the VOI and have furthermore been proven to exhibit at least one of the following modifications with substantial implications on the global public health: rise in transmissibility, adverse effects on Covid-19 epidemiology, increase in virulence or changes in the clinical presentation or a decline of the impact of social distancing and further public health measures or of the available diagnostics, vaccines and therapeutics. (8)

B.1.1.7 (Alpha): This variant was first discovered in the United Kingdom in September 2020 and was one of the dominating lineages world-wide in the first half year of 2021. It is characterized by multiple non-synonymous polymorphisms in the spike protein probably altering e.g. virulence and transmissibility. (4, 8) Infections with the Alpha variant were associated with a higher case fatality rate and a rise in

the reproduction number of about 1.5-fold. (9, 10) Whereas the precise causal mechanisms of these detrimental changes remain unknown, different explanations have been introduced. These include higher angiotensin-converting enzyme 2 (ACE-2) binding affinities, prolonged virus shedding and overall enhanced viral loads in infected individuals. (11, 12)

B.1.351 (Beta): In December 2020, a new lineage was increasingly reported from South Africa presenting with additional non-synonymous mutations in the S-protein. An increased transmissibility and heightened ACE-2 receptor affinity, especially due to combinations of the polymorphisms E484K and N501Y, are under discussion. (13, 14) Additionally it has already been known that the amino acid changes N417 and K484 attenuate the sensitivity of the virus against neutralizing antibodies. (15) In line with this, immune evasion was confirmed by demonstrating absent viral neutralization of convalescent or post-vaccination plasma. (16) Clinical phase 3 trials regarding the vaccine effectiveness also indicated a diminished protecting effect against this lineage. (17)

P.1 (Gamma): This lineage has been detected for the first time in travelers returning from the Brazilian state Amazonas in December 2020 and has shown in further consequence a broad prevalence in whole Brazil. Due to certain spike protein polymorphisms (K417T, E484K, N501Y), this variant resembled the above-mentioned Beta lineage. Arising thereby, greater transmissibility and virulence, as well as a reduced susceptibility to neutralizing antibodies was also presumed in this strain. (2, 18)

However, neither the Beta, nor the Gamma variant became globally dominant.

B.1.617.2 (Delta): While the earliest documented samples from India date back to October 2020, the WHO declared this variant a VOC in May 2021. The variant superseded Alpha as the globally dominating lineage until emergence of the Omicron subtypes. Different spike-protein mutations occurred again in this lineage, with the isolated amino acid exchange L452R showing both higher ACE-2 affinity and enhanced infectivity. (19) In combination with the mutation T478K, the variant exhibits more stable receptor binding domain – ACE-2 complexes further increasing its infectivity rate. (20, 21) Experimental data pointed out that this mutation changes the antigenic features of the virus. Compared to the Alpha variant, Delta variant

boasts greater infection numbers in contact persons and was associated with higher hospitalization rates and more severe disease. Results arising from epidemiological investigations reported a reduced vaccine effectiveness against the Delta variant to prevent symptomatic infection, however the effectiveness against severe disease, hospitalization or death remains high. (22, 23)

B.1.1.529 (Omicron): First reports of the currently dominating SARS-CoV-2 VOC (March 2022) date back to November 2021 from Botswana and South Africa. The first identified sub-lineage BA-1 quickly spread across the globe and replaced the Delta variant as the most prevalent lineage. Besides already known mutations, this variant features numerous new mutations, aggregating to over 30 within the *S* (spike) gene. (24) Many of these changes were previously associated with increased infectivity, transmissibility, and potential immune escape. The amino acid exchanges Q498R and S477N are related to improved ACE-2 binding, which might augment viral infectivity to host cells. (25) First data suggest a replication advantage as analyses indicated an outpacing rise of infection numbers due to Omicron compared to Delta in the United Kingdom. (26) As mentioned above, Omicron is capable of evading the immune system to a larger extent than previous variants. For instance, neutralizing activity against Omicron was partly untraceable in convalescent and post-vaccination sera in some cases of a preprint study. (27) In contrast, observational analyses imply lower risks of severe disease with Omicron infection in relation to preceding variants. (28) As Omicron remained the dominant transmitted variant, subtypes kept on emerging, comprising the descendent lineages BA.1-5 and their sublineages (e.g. BA.2.75), which have been increasingly sequenced globally. (29, 30) Due to the accumulation of additional mutations, the immune evasive traits decreased vaccine efficacy and improved transmissibility in those sublineages. (4) As the viral diversity and its complexity has increased, the WHO added the category “Omicron subvariants under monitoring” to inform public health authorities, which Omicron variants are currently dominating, as well as to swiftly react to further evolutions. (30)

The Centers for Disease Control and Prevention (CDC) expand these classifications of noteworthy variants by a third category, called “Variants of High Consequence”. It would include variants which lead to significantly decreased effectiveness

concerning medical countermeasures and prevention measures, but to date no SARS-CoV-2 lineage is classified in this category. (31)

3.2 Covid-19

The novel disease caused by SARS-CoV-2 was first described in patients suffering from pneumonia. In February 2020 the WHO designated the disease "**Co**rona**vi**rus **d**isease 20**19**". (32) In accordance with rising case numbers, also the variety of clinical manifestations accumulated and with each new sign and symptom clinicians gathered more information about the pathophysiology behind the different disease features. Further investigations and laboratory experiments elucidated the infection in terms of a systemic disease, causing damage not only to the lung tissue, but to several organs of the body. Nevertheless, respiratory symptoms with involvement of the lungs occur most frequently in symptomatic infections.

3.2.1 Epidemiological aspects

The first cases of Covid-19 were reported from Wuhan, the capital city of the province Hubei, in China in December 2019. (6) Subsequently the virus rapidly spread across China and on the 13th of January 2020, the first Covid-19 case outside of China was confirmed in Thailand. (33) Starting from late February, the spread of Covid-19 accelerated all over the world, leading to the declaration of the pandemic since the 11th of March 2020. (34) As of September 2022, over 609 million confirmed cases of Covid-19 occurred, resulting in over 6.5 million deaths around the world, while in contrast an overwhelming 12.6 billion vaccine doses have been administered so far. (35) However, it must be added that both, the reported cases and deaths, underestimate the total numbers by far, because not every infection is diagnosed and reported and not every death is attributed to Covid-19. (36) Seroprevalence studies indicate that the estimated number of unknown cases surpasses the reported cases by approximately 10-fold or more. (37, 38) The assumed median basic reproduction number of SARS-CoV-2 is estimated to amount to 2.4 to 3.9. Median values of 2 to 3.3 are necessary for an exponential increase of infections in the absence of any prevention measures. (39, 40) SARS-CoV-2 infects women and men nearly to the same extent, though it seems that men are at higher risk for severe courses, ending in twice as much deaths.(41) In general,

the risk of severe courses surges in individuals beyond the age of 65, leading to case fatality rates in the subgroup of people above 80 about as high as 20%. (42)

3.2.1.1 Viral Transmission

Transmission via person-to-person is the main infection mode, where three main transmission paths are assumed: droplet infections, airborne infections and direct or indirect contact transmissions. Droplet infections constitute the virus´ primary transmission route and typically take place in the immediate vicinity of infected individuals. (43) Therefore, the risk of transmission peaks within a distance of one to two meters especially in poorly ventilated interiors. (44) These virus-loaded respiratory droplets are produced while breathing, talking, singing and particularly coughing or sneezing. (45) By contact with mucous membranes and inhalation, the virus particles are transmitted to another person. Compared to the larger and heavier respiratory droplets, aerosols hang in the air for extended periods. Subsequently, they potentially infect people especially indoors over greater distances. Although the contribution of airborne transmission to the pandemic is uncertain, investigations propose that it is no primary mode. (46) Transmissions were observed after longer stays in small rooms without air exchange with the risk of contagion increasing over time. (47) The third main transmission route occurs by insertion of virus particles onto mucous membranes after touching contagious surfaces. Typically, these particles originate from respiratory secretions, but SARS-CoV-2 RNA has also been detected in blood, ocular secretions, semen, and stool specimens. In the latter case, viable virus particles were collected in exceptional cases, nonetheless this route is not believed to be of great significance. (48-50) Furthermore, the probability of bloodborne transmission is very unlikely which also applies to infections after virus contact with non-mucous membranes e.g. grazed skin. (51) Vertical SARS-CoV-2 transmissions and infections are possible, albeit they rarely arise in newborns of infected mothers and typically proceed without severe manifestations. These findings support the recommendations that neither SARS-CoV-2 positive mothers nor their babies should be separated from each other, and that breastfeeding is still advised. (52)

Besides person-to-person transmission routes, transmission by animals have been observed aside from the initial spillover to human race. Reported cases occurred in mink farms and lead to the killing of millions of minks in Denmark and the

Netherlands, because of concerns about a new pathogen reservoir. (53) Infections in pets have also been described in households of ill persons, but evidence lacks whether re-transmission to humans are of epidemiological importance or even happened. (54)

3.2.1.2 Infection and Infectiousness

According to a meta-analysis, the mean incubation period is approximately six to seven (6.38) days, with a range between two to almost eighteen days. (55) Mentionable in this context is the index of manifestation, describing the proportion of infected individuals who develop symptoms. To some extent, it is the reciprocal value of all asymptomatic infection which constitute at least one third. Thereby, only about 66% of infected people really fall ill with Covid-19. (56)

Transmissions by symptomatic individuals are suggested to represent the majority of the overall transmission rates. (57) However, transmissions are not restricted to symptomatic cases but can occur via asymptomatic individuals. Hence, presymptomatic and asymptomatic persons can be contagious. (58) One study even estimated an amount of presymptomatic transmissions of 44%. (59) True asymptomatic cases, who never develop symptoms, seem to comprise a cohort of reduced contagiousness, with lower secondary attack rates, compared to symptomatic individuals. (60) The time in which infected persons show the greatest infectiousness is probably between two days before onset of symptoms and one day thereafter with consequent decreases during the first week. (59) Hence, transmission seven to ten days after disease onset is unlikely, especially in immunocompetent patients with mild to moderate infection. (61) The finding that viral RNA shedding is not necessarily associated with infectiousness is of great importance. In many cases, RNA can be traced weeks after cessation of symptoms, but to a considerable degree no viable infectious viruses are detected in those individuals. This indicates the existence of a certain threshold of viral RNA levels, underneath which infectiousness is not likely. (62-64)

3.2.1.3 Risk factors for severe disease

Severe courses of Covid-19 occur across all age groups. Only with the development and utilization of effective vaccines and Covid-19 specific treatments, the risk of severe disease and ICU admission decreases. Hospitalization, admission to the ICU, mechanical ventilation and death are common outcomes to define severe

illness. (65) Advanced age is one of the major risk factors of severe progressions. Cohort studies revealed that the strongest associated risk factor for death was age beyond 80 years. (66) Patients of the age of 80 or older experienced a 20-fold increased risk of death when compared with individuals between 50 to 59 years. (67) Data from a meta-analysis further support these findings revealing age >75 years as an important risk for severe Covid-19 disease. (68) A meta-analysis on the aforementioned differences between female and male sex concluded that the probability of death among men with Covid-19 is raised by 61% compared to female. Additionally, the chance of severe disease is increased in men, in combination with significantly lower recovery rates. (41) Beside advanced age and male sex, comorbidities further aggravate the risk for severe disease with mortality rising with the number of comorbidities. (66) The CDC has compiled an updated list of comorbidities associated with a high risk for severe outcomes in Covid-19, which assorted the underlying conditions according to the existing level of evidence. The first group is composed of comorbidities which show significant associations with the risk of severe illness endorsed by at least one meta-analysis or systematic review. It contains cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, cardiac diseases (such as coronary artery disease, cardiomyopathies or heart failure), obesity, pregnancy or recent pregnancy and former or current tobacco abuse. Underlying diseases allocated to the second group are mainly supported by observational studies. Trisomy 21, human immunodeficiency virus (HIV), neurologic conditions (e.g. dementia), sickle cell disease and immunosuppressive states (including solid organ or blood stem cell transplantation and immunosuppressive medications) constitute the second category. In contrast, the evidence for hypertension, immune deficiencies or liver diseases as risk factors diverges between studies. (65) Also genetic factors are believed to affect the course of disease. One example is the relationship between respiratory failure and a higher risk for patients with blood group A of the AB0-system, while type 0 is not only associated with a decreased risk of severe disease but also infection itself. (69, 70) Beyond that, other genetic factors might play a role in susceptibility to severe courses of Covid-19 and need further investigation.

3.2.2 Viral life cycle and pathophysiology

After SARS-CoV-2 has entered the body through mucous membranes, it invades its host cells by endocytosis or membrane fusion. The spike protein has been identified as the crucial component of this fundamental step to infect susceptible cells. Furthermore, the presence of ACE-2 on the cell surfaces, which serves as the receptor for the S1 domain of the spike protein, is crucial. The S1 domain with its specific receptor-binding domain is located on the uncovered surface of the viral spikes, enabling direct interaction with ACE-2. This interaction is the initial phase of adsorption of SARS-CoV-2 into the host cell membrane and defines the typical tropism of the virus solely infecting ACE-2 positive cells by this receptor-mediated mechanism. (71, 72) In the next stage, the virus penetrates the host cell via one of two different pathways, already mentioned above. If the virus enters by membrane fusion, the host cell transmembrane protease serine subtype 2 (TMPRSS2) is involved in the process. TMPRSS2 mediates the so-called S protein priming, leading to a proteolytic cleavage of the spike protein into the domains S1 and S2, which activates the viral protein. After cleaving off the S1 domain and a small part of the S2 domain, the fusion protein of the S2 domain remains, which is then inserted into the host cell membrane. This finally enables the virus particle to merge with the cell membrane, leading to the release of viral RNA into the cytoplasm. (71) The second pathway is receptor-mediated endocytosis. This absorption of the virus into the host cell is driven via a clathrin-dependent or -independent endocytosis. (73, 74)

After uncoating, the viral genomic RNA is translated into proteins using ribosomes in the cytoplasm of the host cell. This direct translation is enabled by the ss+ RNA genome of the coronavirus. As a result, different structural and non-structural proteins, including the RNA-dependent RNA-polymerase (RdRp), are produced. Together with other non-structural proteins, the RdRp forms the replicase-transcriptase complex, which synthesizes viral RNA and mRNA leading to the formation of virus elements in larger quantities. After assembling the components to new viable progeny, they leave the host cell by exocytosis with the ability to infect further cells. (39, 75) Concerning the tropism of the virus, ACE-2 expressing cell types were found throughout the body, including nasal and oral mucosa, nasopharynx, both alveolar epithelial cell types (pneumocytes I and II), enterocytes of the small intestine, the skin, smooth muscle cells and, interestingly, in most arterial and venous endothelial cells. (76) These findings could explain the

heterogenous signs and symptoms of Covid-19 as well as the involvement of different organs.

Following infection, SARS-CoV-2 starts replicating in epithelial cells of the upper respiratory tract. (77) This could also explain the high viral loads in this region, which is associated with greater transmissibility. (77-79) Subsequently, the virus migrates to the lower respiratory tract, until it reaches the lungs infecting type II pneumocytes. (80) This leads to the decay of this cell type by apoptosis and pyroptosis. (81, 82) Combined with an activation of alveolar macrophages, these processes possess substantial pathophysiologic relevance by triggering immunologic dyshomeostasis in the lung tissue of infected individuals. (83) Following activation, a multitude of pro-inflammatory cytokines and chemokines, including interleukin (IL)-1 beta, IL-6, IL-8 and tumor-necrosis-factor-α (TNF-α), are secreted into the pulmonary tissue and vasculature by the alveolar macrophages. (84) These mechanisms yield the activation of vascular endothelial cells, which in turn result in the mobilization of a magnitude of different immune cells, comprising cytotoxic neutrophils as well as inflammatory activated platelets into the alveolar space. These pro-inflammatory processes play a major role in the pathogenesis of Covid-19 in general and specifically in the development of acute respiratory distress syndrome (ARDS). (85, 86) Moreover, the excessive release of IL-6 is a driving component of the so-called cytokine storm and is jointly responsible for the development of sepsis-related dysregulations of the immune response. (87, 88) Studies showed that especially IL-6 and IL-10 are highly increased in severe cases of Covid-19 which are further supported by data suggesting IL-6 levels correlate positively with Covid-19 severity and mortality. (89-91)

3.2.2.1 Immune response and Immunity

After infection with SARS-CoV-2, humoral and cell-based immune responses are evoked. Regarding the humoral immune response, detectable immunoglobulin (Ig)M antibodies emerge between eight to twelve days following onset of symptoms and seem to vanish after twelve weeks. Seroconversion of IgG antibodies ensues shortly thereafter with a mean of 14 days but remain longer and correlate with disease severity and the viral load. (92, 93) Also neutralizing antibodies regularly occur at the end of week two, although their titers apparently fade over time, especially after mild or asymptomatic infections. (94, 95) Despite the decline of

antibody titers, it is assumed that neutralizing activity is retained for up to six to eight months. (96, 97) Studies suggest that neutralizing antibodies are related to a protection at least against severe reinfections with current SARS-CoV-2 lineages, but the protective capability against future variants remains questionable. (98, 99) Besides antibody producing plasma cells, further cells of the immune system establish the cell-mediated immunity after contracting Covid-19. This includes SARS-CoV-2-specific memory B, CD4+ T cells and CD8+ T cells. Gathering information about the longevity of memory cells is of great interest to draw conclusions regarding the durability of protective immunity against SARS-CoV-2. To date, research on this topic is ongoing and current results need to be evaluated and confirmed by future studies. One study examined the kinetics of the main memory cells for up to eight months, starting from infection. Results displayed an increase of memory B cells between month one and eight, whereas memory CD4+ and CD8+ T cells diminished in the same period with an initial half-life of three to five months. The percentage of study participants with traceable SARS-CoV-2 memory CD8+ T cells 30 days after infection reached approximately 70% and dropped to about 50% after six to eight months. The amount of CD4+ T memory cells persisted on a high level over the same period, with 93% of participants after the first month and 92% after more than six months, respectively. They concluded that just above 95% of subjects preserved at least three of the main types of immune memory up to six to eight months after contracting SARS-CoV-2. However, it needs to be elucidated to which extent these findings indicate protection against reinfections. (96) Data revealed that the risk of reinfection is reduced by 80 to 85% within the first six to nine months after initial infection. (99, 100) However this risk reduction declined since the emergence of the Omicron variants. (101)

3.2.3 Clinical presentation

SARS-CoV-2 presents with a wide variety of clinical signs and symptoms and degrees of severity. For that reason, the National Institute of Health (NIH) subdivides Covid-19 illness into five distinct groups. The spectrum ranges from asymptomatic cases over mild and moderate diseases to severe and critical Covid-19 illness. Mild illness covers symptoms typically reported from outpatient Covid-19 cases, including fever, cough, myalgia, malaise, or nausea, but in the absence of shortness of breath, dyspnea, or abnormal chest imaging. Moderate cases show signs of lower

respiratory tract infection during clinical evaluation or imaging combined with oxygen saturations (SpO_2) of at least 94% on ambient air. Individuals with severe onset of Covid-19 either show SpO_2 values below 94% on ambient air, respiratory rates above 30 breaths per minute, a ratio of arterial blood oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2, oxygenation index) <300 mmHg or lung infiltrates >50%. Critical cases include patients who suffer from respiratory failure, multiple organ dysfunction, and/or septic shock. (102) Another report estimated the frequencies of each category: 81% have mild or moderate disease, 14% present with severe manifestations and 5% were reported to suffer from critical illness. The overall case fatality rate was declared with 2.3%, without any deaths resulting from noncritical cases. (103) Further analyses revealed hospitalization rates of 14% and intensive care unit (ICU) admissions were necessary in about 2% of affected persons. The risk for hospitalization increased six times in the presence of underlying conditions and led to a twelve times higher mortality rate in this patient population compared to patients without pre-existing disease. (104) In the same case survey, the prevalence of different symptoms in confirmed Covid-19 cases were analyzed, with cough being most frequently mentioned with 50%. It was followed by fever and myalgia in 43% and 36% of patients, respectively. Moreover, 34% or 29% of persons complained about headache and subjective shortness of breath (i.e. dyspnea). Gastrointestinal symptoms included diarrhea (19%), nausea or vomiting (12%) and abdominal pain (<10%). Common otorhinolaryngological symptoms included sore throat in 20%, and less common (each <10%) loss of smell or taste or rhinorrhea. Dermatologic findings can occur throughout the course of infection, with various different rashes described to date, albeit they are mostly nonspecific and rare (0,2-1,2%). (105) Efflorescences range from erythema to vesicular, urticarial, or maculopapular lesions to transient livedo reticularis and in some cases chilblain-like eruptions have been described. (106) While the most common severe manifestation described is pneumonia, typically appearing around day four after onset of symptoms, its main complication is progression to ARDS, which develops on average eight days after initial manifestation. (104, 107, 108) Cardiac involvement in Covid-19 includes myocarditis, cardiac insufficiency, and arrhythmias by myocardial injury and infarction. Thromboembolic events are well known complications and venous thromboembolism (VTE) commonly manifests in form of deep vein thrombosis (DVT) with subsequent PE, while arterial embolisms

result in stroke, acute limb or mesenterial ischemia. (109, 110) Covid-19 related vasculopathies are further described below. Besides strokes, additional neurological complications were observed in Covid-19, including encephalopathies, which were notified in one third of hospitalized patients, as well as ataxia, movement disorders, seizures and Guillain-Barré syndrome, all with lower frequencies. (111, 112) Hyperinflammatory responses, like the aforementioned cytokine storm, mainly occur in patients with severe illness and are characterized by exaggerated levels of pro-inflammatory cytokines and inflammatory markers (e.g. ferritin and D-dimer) with enduring fever. (113, 114) Secondary infections complicate the course of disease with reported rates of approximately 8%. Investigations detected different species of bacteria and fungi (especially aspergillus and mucorales species), particularly in severe cases of Covid-19. (115-117)

3.2.4 Diagnosis

Blood sample analysis of hospitalized Covid-19 patients revealed lymphopenia and elevated levels of inflammatory markers, such as C-reactive protein (CRP), ferritin, erythrocyte sedimentation rate (ESR), and of lactate dehydrogenase (LDH). Furthermore, elevated transferase levels and alterations in coagulation tests were observed as typical laboratory constellations in this patient population. D-dimer and fibrinogen levels are typically elevated in hospitalized patients, while platelet counts can range from severe thrombocytopenia to thrombocytosis. Additional main parameters include the activated partial thromboplastin time (aPTT) and prothrombin time (PT), which are frequently prolonged. At admission, values of the international normalized ratio (INR) were predominantly within the normal range. (118-120) Moreover, elevated levels of myocardial enzymes are regularly detected. (108, 121, 122) Despite the very common lymphopenia, white blood cell (WBC) counts can range from leukopenia to leukocytosis. (122) Another parameter of interest is procalcitonin which seems to be elevated more likely in severe cases involving ICU admission. (114)

In addition to laboratory findings, imaging methods reveal Covid-19 related pathologies and are therefore of great importance in the course of diagnosis, management, therapy and follow-up. (123) The following paragraph describes imaging modalities to objectify pulmonary manifestations of Covid-19, while imaging procedures in respect of thromboembolic vasculopathies are described elsewhere

(3.3.3.1). The commonly performed chest X-ray might show no pathologies during early stages of disease, but typical findings become apparent with disease progression. These encompass bilateral and multifocal, peripheral alveolar opacities and consolidations, predominantly in the lower lobes. (123-125) If a computed tomography (CT) of the chest is performed, the images often show ground-glass opacities with or without consolidated areas, mainly in peripheral or subpleural areas. Additional pathologies include adjacent pleural thickening, interlobular septal thickening, or air bronchograms, besides less frequent findings. (123, 126) Ultrasonography of the lungs is another option to quickly assess the pulmonary involvement with sensitivity and specificity reaching 86% and 55%, respectively. (127) Ultrasonography may reveal thickened, irregular, and discontinuous pleural lines and B lines below the pleura, which arise discrete, multifocal, or confluent. Air bronchograms within consolidations and perilesional pleural effusions might be detected in all described techniques. (123, 128, 129)

Besides the already known clinical, laboratory or imaging manifestations, leading towards the diagnosis of Covid-19, further confirmatory tests are necessary. The fact that no clinical feature can reliably distinguish Covid-19 from other infectious diseases and pathologies, direct and indirect virus detection methods are essential to make a definitive diagnosis. (130, 131) To detect current infections with SARS-CoV-2, nucleic acid amplification tests (NAATs) are the microbiologic tests of choice, especially reverse-transcriptase polymerase chain reaction (RT-PCR). A variety of different RT-PCR assays are in use, which partly amplify and detect different regions of the SARS-CoV-2 RNA genome. The envelope (*E*), nucleocapsid (*N*), spike (*S*) or *RdRp* genes are commonly selected targets, and often more than one sequence is amplified by the various NAATs. (132) The performance of a RT-PCR following collection of a specimen from the upper respiratory tract is the preferred initial procedure to detect viral RNA. (133) Upper respiratory tract samples are obtained from nasopharyngeal, nasal middle turbinate or nasal swab specimen of both anterior nares, apart from oropharyngeal swabs and saliva specimen, to mention the most important. (134) When comparing the sensitivity of the different specimens, data suggests that nasal, nasopharyngeal and saliva samples outperform oropharyngeal swabs. (135, 136) Besides the upper respiratory tract, also samples from the lower airways can be collected, e.g. from sputum or bronchoalveolar lavage, resulting in higher rates of positive tests. (135, 137) Aside

from the type of specimen, the sampling time relative to disease duration also affects the test performance. With rising viral loads in the upper airways, also the probability of a true positive result increases, leading to the assumption that RT-PCR reliability peaks within the first three days after initial symptoms. (93) The overall sensitivity and specificity concerning standard laboratory-based NAATs were 98% and ≥97%, respectively. (136) Under standard conditions, a positive NAAT result suffices to confirm the diagnosis Covid-19, with no additional tests indicated. If a test is negative, but a strong suspicion for SARS-CoV-2 infection remains, it is recommended to repeat the NAAT after 24 to 48 hours. (131)

The detection of SARS-CoV-2 antigens is another microbiologic test opportunity to identify individuals with Covid-19. The benefits are the rapid performance and fast interpretation of results, compared to RT-PCR. Antigen tests are especially adequate to confirm the diagnosis in symptomatic patients. By contrast, sensitivity of antigen tests is known to be inferior to NAATs, while specificity surpasses 99%. (138, 139) Therefore, a negative result should be confirmed with a NAAT with superior sensitivity in all symptomatic cases, at best within 48 hours. (140) In general, these tests detect the presence of an antigen via specific antibody-antigen-binding and further visualize this reaction. Most SARS-CoV-2 antigen kits use antibodies targeting the N protein, because of its abundance during virus replication and the low cross-reactivity with other coronaviruses. (141-143)

Measurement of circulating antibodies in the blood is the third approach to diagnose Covid-19, especially to detect prior or late infection. After a time span of approximately two weeks from initial symptom onset, antibodies are detected. (144) These tests use different platforms to detect SARS-CoV-2-specific antibodies, e.g. lateral flow immunoassays (LFIA), enzyme-linked immunosorbent assays (ELISA) and chemiluminescent immunoassays (CLIA). (145) At the moment, mainly the spike and nucleocapsid proteins of SARS-CoV-2 are used in antibody assays to identify specific antibodies in sera. (146) Additionally, it is recommended to use test kits of superior accuracy, namely IgG or total antibody tests, rather than IgM, IgA or IgM/IgG differentiation tests. (147)

Noteworthy, the ongoing evolution of SARS-CoV-2 variants could influence test performances as new mutations, especially in the N and S genes may become undetectable for certain test kits and RT-PCR. (148, 149)

3.2.5 Patient management and therapeutic approach

Since the majority of Covid-19 cases only develop mild symptoms, outpatient care is often sufficient. Patients with mild illness do not suffer from hypoxemia or pneumonia and therefore admission to hospital is typically unnecessary. (104, 150) Symptoms of a severe course, including dyspnea, oxygen saturation ≤94% on ambient air, dizziness, confusion or altered mental state warrant inpatient evaluation. In the presence of comorbidities known to increase the risk for severe Covid-19 and in older patients, individual decisions are required, whether admission is indicated. (150) If the condition allows outpatient management, the patients should be briefed how to react in case of disease progression. Especially, if the clinical status worsens with the onset of dyspnea, fever beyond >37.5 °C, increased chest pain or tightness, patients are advised to contact their health care provider or hospital for further assessment. (39, 151, 152) These symptoms also indicate the spread of the virus to the lower respiratory tract. In this case, self-monitoring of SpO_2 values with pulse oximeters can serve as a decision support in combination with the patient´s overall clinical condition. (153) To manage their symptoms, outpatients can be advised to take over-the-counter analgesics, antipyretics and antitussives depending on their afflictions. General recommendations involve adequate liquid intake, reasonable exercise and rest. (150) The use of Covid-19 specific therapies can attenuate disease progression to severe Covid-19 manifestations or hospitalization. Hence, administration of these drugs is recommended in mild to moderate Covid-19 cases with risk factors for severe disease. The recommended therapies include the oral protease inhibitors combination product nirmatrelvir-ritonavir (Paxlovid) and current anti-SARS-CoV-2 monoclonal antibodies. An effective monoclonal antibody therapy neutralizing Delta and Omicron is bebtelovimab. Treatments should be initiated at the earliest opportunity after SARS-CoV-2 infection is confirmed. (150, 154, 155) In view of infection control, infected individuals are constrained to minimize their social interactions and stay isolated, especially during the acute phase of the disease. As quarantine regulations differ between countries, no uniform guidelines are implemented.

In contrast to the common mild and moderate illnesses, severe courses of Covid-19 warrant intensified treatment. As previously mentioned, certain clinical findings are indicative of disease progression or severe disease. Patients who present with fever >37.5°C, dyspnea/respiratory rate >22/min or oxygen saturation ≤94% on ambient

air combined with further suspicious clinical findings upon examination are in need of admission to hospital. (39) For this purpose, evaluation of vital parameters (i.e., respiratory rate, SpO_2 values, body temperature, heart rate and blood pressure) is essential in Covid-19. During the initial assessment of this patient population, different scores may facilitate the decision making. The Quick Sequential Organ Failure Assessment (qSOFA) score, as a fast and easy applicable tool, can be promptly used by clinicians to examine the patient's organ functions regarding potential sepsis. A Covid-19 specific score is the ISARIC-4C to evaluate mortality, enabling the stratification of patients into different management groups. The score ranges from 0 to 21 points and is calculated based on eight parameters. (39, 156) During the course of clinical assessment, the following laboratory markers should be ascertained: complete blood count with differential, creatine kinase, CRP and a comprehensive metabolic panel. Besides CRP, additional inflammatory parameters can be obtained including procalcitonin or ferritin as acute phase proteins. Initial laboratory findings to analyze the coagulation system, including PT, aPTT, fibrinogen and D-dimer, are also recommended in patients with Covid-19. Regarding renal parameters, urinalysis (checking for albuminuria, hematuria or leukocyturia) allows a more precise assessment of the renal function. Elevated levels of LDH and troponin can indicate severe disease progression and should be therefore also measured. Arterial blood gas analysis provides not only deeper insights into the current pulmonary situation of the patient in addition to pulse oximetry, but also reflects the acid-base balance. (39, 157) The received PaO_2 also serves to calculate the oxygenation index. This index is recommended to assess the extent of a potential acute lung injury, which also influences the therapeutic process. (158)

Depending on the severity of the acute hypoxemic respiratory failure, different therapeutic approaches regarding the oxygen therapy are indicated. If conventional oxygen therapy fails to achieve adequate oxygenation saturations, high-flow nasal cannula (HFNC) oxygen is the next step in escalating therapy. HFNC is favored over noninvasive positive pressure ventilation in patients with an oxygenation index between 100 to 300 mmHg. (150) These interventions should only be implemented under continuous monitoring in an intensive care unit. In accordance with that, the S3 guidelines of the "Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften" recommend transfer to the intensive care unit of patients suffering from hypoxemia with SpO_2 values below 90%, who receive 2-4 L/min of

oxygen (without preexisting therapy) or respiratory rates beyond 25-30/min. Continuous monitoring is essential as the respiratory status of Covid-19 patients may deteriorate, leading to acute respiratory distress syndrome, which also includes the permanent standby to intubate. (150, 158, 159) Prone positioning of patients, who are not intubated, is another potential therapeutic approach. Oxygenation indexes often improve, but current trials could not show a reduction of intubation rates after the temporary change of position. Consequently, additional studies are necessary to determine which patients benefit most. (160-162) If the respiratory situation aggravates further with PaO_2/FiO_2 values dropping below 100 mmHg, intubation is advised in a routine setting by a skilled physician, followed by invasive mechanical ventilation. (159) So far, the ventilation strategy of Covid-19 associated ARDS is comparable to other ARDS cases. Guidelines advocate a low tidal volume with 4-8 mL/kg predicted body weight and plateau pressures not exceeding 30 cmH_2O. (150, 159, 163) Moreover, higher positive end-expiratory pressures (PEEP) are preferred over lower values with a cut off at approximately >10 cmH_2O. Prone positioned ventilation for 16 hours per day may benefit the ventilation therapy. In severe cases of ARDS, extracorporeal membrane oxygenation (ECMO) is the last step of therapy escalation in otherwise not manageable respiratory failure. (164) The general, therapeutic target in Covid-19 patients suffering from acute hypoxemic respiratory failure is to restore adequate oxygenation with SpO_2 reaching ≥90% (in patients with COPD >88%) and PaO_2 >55 mmHg, respectively. (159, 165) As a fundamental rule in patients with acute respiratory failure conservative fluid strategy is pursued. (150)

As venous thromboembolic events are frequently reported in Covid-19, administration of prophylactic dose anticoagulation is pivotal in all hospitalized, adult patients in the absence of contraindications to reduce the risk of aggravating complications. Low molecular weight heparin (LMWH) is the preferred prophylactic medication, while fondaparinux serves as an alternative in patients with heparin intolerance. (166) Intensified thromboprophylaxis is indicated in cases with additional risk factors for VTE, in particular obesity (body mass index [BMI] >35 kg/m^2), known thrombophilia, previous VTE, intensive care treatment or markedly elevated D-dimer levels (>2-3 mg/L). (167) Besides the pulmonary and vascular system, additional organs are afflicted in Covid-19. In severe cases, acute kidney injury has been observed necessitating the use of continuous renal replacement

therapy. (150) Although the frequency of superinfection is not exactly known due to limited data, bacterial as well as fungal coinfections complicate courses. Especially the already affected lungs are susceptible to superinfections, resulting in bacterial pneumonia or pulmonary aspergillosis. Therefore, antibiotic, and antifungal treatment may be indicated in selected individuals. If bacterial sepsis is assumed, patients receive empiric antibiotic therapy followed by reevaluations of the clinical course on a daily basis and adjustment of the therapy when the responsible pathogen is detected. (39, 150) In general, at least two blood cultures (for aerobic and anerobic bacteria) should be obtained once patients are admitted to the ICU or if the patient´s state deteriorates. (168) Elevated procalcitonin is indicative of bacterial superinfection, besides serving as a marker to detect severe Covid-19 cases. (169)

As mentioned above, the leading processes in the development of Covid-19 are viral replication at initial stages of disease, followed by a dysregulated immune response in severe illness. Because these major mechanisms forge disease progression, they are also targets of medical interventions. (150) This leads to the two main drug treatment approaches: antiviral and immunomodulatory therapies. (158) So far, Covid-19 specific drug regimens still evolve. One of the first Covid-19 approved antivirals was remdesivir. Albeit trial results diverge, remdesivir has shown to reduce time to recovery and discharge from hospital in the subgroup of patients who only required low flow rates of oxygen therapy. (170) A meta-analysis, on the contrary, revealed no significant advantage of remdesivir over the standard treatment regarding 28-day mortality. (171) In patients, who depend on high flow oxygen devices, it is suggested to administer remdesivir only in combination with the glucocorticoid dexamethasone. While dexamethasone is not administered in mild to moderate Covid-19 cases, it is highly recommended in all patients with severe to critical illness, in the absence of contraindications. Data indicate a reduction of 28-day mortality in hospitalized patients with increasing therapeutic effects in more severe courses. (158) Intubated patients benefit most from dexamethasone with an absolute mortality reduction of 12% (172) A restricted therapy recommendation exists for the monoclonal anti-interleukin-6 receptor antibody tocilizumab, which is administered as a single dose and combined with glucocorticoid treatment. Additionally, it is merely endorsed in Covid-19 cases with systemic inflammation (CRP >75 mg/L), experiencing progressive oxygen therapy dependency or have

been mechanically ventilated for less than 24 hours. (173) A multitude of other drugs are currently under evaluation in clinical trials for the treatment of Covid-19. Camostat, a serine protease inhibitor, might be able to prevent SARS-CoV-2 cell entry via the blockage of TMPRSS2. (174) The janus kinase inhibitor baricitinib is another treatment candidate, who is assumed to inhibit immune activation and inflammation of cells to a certain degree. It is already in clinical use after the U.S. Food and Drug Administration announced an emergency use authorization in combination with remdesivir in hospitalized patients who require supplemental oxygen. Moreover, data also suggest a benefit for patients without invasive mechanical ventilation in combination with remdesivir and/or dexamethasone, reducing 60-day mortality. (175, 176) In general, Covid-19 patients with concomitant medications for the treatment of underlying diseases should take their medicine as prescribed (e.g. ACE-inhibitors, angiotensin receptor blockers, statins, systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs or acid-suppressive therapy). (150)

3.2.6 Prevention

Preventive steps are essential to reduce the risk of infection throughout the population, especially in regions where community transmission of SARS-CoV-2 is present or on the rise. Social distancing with the avoidance of gatherings as well as keeping distance (≥2 meters) to other people rank among the most important measures to disrupt the chain of infection. (2, 177) Intensified hand hygiene is appropriate throughout the pandemic and should be performed thoroughly after contact with potentially infectious surfaces or individuals using soap and/or sanitizer. Covering the mouth while coughing and sneezing without contaminating the hands (e.g. via the cubital fossa or a tissue) is part of the respiratory etiquette and another advised personal preventive measure. To reduce aerosols potentially containing viable SARS-CoV-2 particles in interior spaces, appropriate exchange of air is suggested via aeration, fans, air conditioning or special air filtration systems. (39, 178) Wearing masks in public can efficiently reduce the secretion of droplets into the environment and the risk of becoming infected, particularly indoor or if maintaining adequate distances is not possible. (39, 179) The recommended type of mask (cloth-, disposable face mask or medical respirators) depends on the institution and setting, but probably more important than the type is the correct

usage. While masks should fit closely over nose and mouth, contamination of the mask (e.g. via hands) has to be avoided and the regular exchange of the mask is considerable. (180) Different public health strategies are also able to contain transmission rates. Implementation of serial testing facilitates the detection of SARS-CoV-2 infections in regions of high prevalence and therefore prevents further infections or outbreaks. Both NAAT and antigen tests are appropriate for the conduct of population screenings. (181, 182) Whenever a person tested positive for SARS-CoV-2, the person is required to go into self-isolation, unless medical attendance is needed. Only in the event of excessive infection numbers, key professions to maintain essential facilities may be exempt from quarantine.

As soon as housemates are in the same room with isolated persons both should wear masks at all time. (183) More drastic interventions range from the closure of non-essential businesses or educational institutions, to the limitation of public gatherings and events through to curfews and travel restrictions, which have been realized in many countries around the world. (2, 39)

With the aid of vaccines, the pandemic is better controlled and less patients die from infections. Therefore, vaccines are numbered among the most promising approaches to end the pandemic. Six vaccines are currently approved in the European Union, including two mRNA, two viral vector, one inactivated, adjuvanted whole virus, and one protein-based vaccine, while additional candidates are frequently evaluated or under rolling review. (184) In addition, adapted vaccines against omicron subvariants have been developed, with the “Comirnaty Original/Omicron BA.4-5” adapted vaccine being the latest on the market. If enough doses are available, which are accessible for everyone in every part of the globe, and the percentage of people willed to get vaccinated is high enough, the herd immunity could potentially terminate the ongoing infection events. Tedros Ghebreyesus, Director-General of the WHO, clarifies: “The pandemic will not be over anywhere, until it´s over everywhere.” (185)

3.2.7 Covid-19 in childhood

The following paragraph solely covers the main topics to give a short overview on SARS-CoV-2 infections in children. Equally to adults, also children and adolescents of every age are susceptible to infections with SARS-CoV-2. However, it is assumed that the extent of susceptibility is less marked. (186) Children transmit SARS-CoV-

2 efficiently to other children and family members and apparently shed virus with comparable or higher virus loads as opposed to adults. (187-189) Asymptomatic SARS-CoV-2 infections occur in 15-42% of cases in childhood, but if infections are symptomatic, the course of disease is mostly mild. (190, 191) Severe manifestations are rare, but typically affect young infants and children with underlying diseases, most important pulmonary and cardiac conditions. (192) In a study evaluating risk factors for admission to the intensive care unit, age below one-month, pre-existing diseases and signs of lower respiratory tract infection were identified. (193) A severe complications encountered is the “Multisystem Inflammatory Syndrome – in children” (MIS-C), which is also known as “Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection” (PIMS-TS), which usually appear two to four weeks after infection with SARS-CoV-2. (194, 195)

3.3 Vasculopathies

Vasculopathy refers to all diseases, which affect the vascular system. Vascular abnormalities can originate from congenital, metabolic, degenerative, or inflammatory disorders, yielding coagulative or thromboembolic conditions. (196, 197) Degeneration is often induced by arteriosclerotic lesions, such as atherosclerosis of the vessel walls, while infectious and noninfectious vasculitides trigger inflammatory vascular changes. Hence, these miscellaneous diseases are either categorized as non-inflammatory or inflammatory vasculopathy, also in this thesis. Additional classification criteria involve the predominantly affected vessel type (arteries or veins) and size (large, medium, or small vessels). Moreover, these vascular disorders promote the formation of and risk for thromboembolism, which occurs in both, the arterial and venous vasculature and represents a major complication of vasculopathies.

3.3.1 Non-inflammatory vasculopathies

This term comprises vascular diseases in which inflammation is not the primary cause. Of the various entities, arteriosclerotic lesions rank among the most important, as they also serve as starting points for frequently devastating diseases. Besides, also venous, and congenital or acquired aneurysmatic diseases are numbered among this extensive term. In the following, emphasis is laid on arteriosclerotic changes. The pathological processes of arteriosclerosis take place

in the inner (intima), as well as the middle (tunica media) layer of arteries. While some changes already develop during childhood and progress over time, others typically evolve in adults of advanced age with or without accompanying comorbidities. (198) Thereby, arteriosclerosis and its complications significantly affect the risk of cardiovascular events.

3.3.1.1 Arteriosclerosis

Arteriosclerosis generally refers to hardening and stiffening of arteries. It thereby represents the umbrella term for specific arterial diseases, which result in vascular remodeling in response to pathologic conditions and triggers. Consequently, arterial walls thicken and lose their elasticity, typically leading to progressive narrowing of the vessel lumen. The multifactorial etiology of arteriosclerosis combines genetic predisposition, chronic and systemic inflammatory diseases, and lifestyle factors, including nutrition, physical activity, and tobacco abuse. This indicates that advanced age is the common risk factor for all arteriosclerotic diseases, as vascular lesions accumulate during a lifetime. Currently, the classification of arteriosclerosis differentiates four distinct diseases: atherosclerosis, Mönckeberg's medial sclerosis, fibromuscular intimal hyperplasia, and arteriolosclerosis. (198-201)

3.3.1.1.1 Atherosclerosis

Among the four lesions, atherosclerosis is the most frequent and clinically significant manifestation, primarily responsible for millions of deaths worldwide each year. It affects elastic and muscular medium and large arteries and originates from lipid and cell debris deposits in the tunica intima, thereby building the characteristic atheroma or atherosclerotic plaque. Their lipid core predominantly consists of cholesterol and cholesterol esters with necrotic cell debris of inflammatory cells. Connective tissues and extracellular components such as matrix proteins, enzymes, and calcium deposits are found within the atheroma. A fibrous cap covers the core and extends into the arterial lumen as the lesion increases in size. (198, 200, 201) To date, the “response-to-injury hypothesis” is the generally accepted model for the pathogenesis of atherosclerosis. Hemodynamic disturbances due to increased shear conditions, especially at branch points, further aggravated by arterial hypertension, in combination with hypercholesterolemia, represent key pathogenic factors. Both trigger endothelial injury leading to endothelial dysfunction, which results in increased permeability, leukocyte adhesion, and thrombosis. Following

accumulation of lipoproteins (primarily oxidized low-density lipoprotein [LDL] and cholesterol crystals) within the intima, adhered and migrated monocytes differentiate into macrophages in the intimal lesion. By phagocytizing oxidized lipoproteins and cholesterol crystals, macrophages become foam cells, which maintain an inflammatory milieu by continuous release of cytokines. Simultaneously, chemokines and growth factors released by macrophages and endothelial cells induce smooth muscle cell (SMC) proliferation and recruitment to the intima. Their production of extracellular matrix substantially contributes to the formation of a mature atherosclerotic plaque. The result is a chronic inflammatory state with ongoing enlargement and cell decay, potentially leading to the atheroma's devastating complications. (198, 201) The morphologic correlates of atherosclerosis begin with the formation of fatty streaks, developing from small, yellow spots in the level of the intima to the characteristic streaks. Mature atherosclerotic plaques appear as elevated white to pale yellow lesions, which protrude into the vascular lumen. Continuous evolution and remodeling of the atherosclerotic lesion also includes the apoptosis of SMC and the breakdown of stabilizing matrix, resulting in the formation of a vulnerable plaque. These are prone to rupture, ulceration, or erosion and may become clinically evident after thrombus formation with signs of ischemia distal to the event. The most frequent chronic sequela is peripheral arterial disease (PAD). Moreover, aneurysms can also develop at the site of severe atherosclerotic plaques through disrupting the perfusion of the underlying tunica media and inflammatory changes in the extracellular matrix. Both cause weaking of the media´s integrity, giving rise to aneurysmatic expansion. (199, 201) Thereby, the sequelae of atherosclerosis are the leading causes of mortality and morbidity among industrialized countries.

3.3.1.1.2 Mönckeberg´s medial sclerosis

This disease describes a calcification process within the tunica media, as well as the internal elastic lamina (outermost layer of the intima), which typically occurs in muscular medium- to large-sized arteries of the extremities and genital tract. It is typically associated with type 2 diabetes and end-stage renal disease and is rarely encountered in patients younger than 50 years. Vascular calcific deposits are crystalized and consist of hydroxyapatite. Presumed mechanisms involved in this process are changes in calcium and phosphor serum concentrations, in combination

with oxidative stress, and locally generated hydrogen peroxide in the vessel wall. These trigger the differentiation of SMC into an osteogenic phenotype and negatively affect inhibitors of calcification. Affected arteries appear corrugated, sometimes resembling cartilages of the trachea. (198, 199, 201) Though Mönckeberg´s medial sclerosis itself does not narrow the arterial lumen, it complicates the diagnosis of PAD, due to the calcified, incompressible media.

3.3.1.1.3 Arteriolosclerosis

Compared to the aforementioned, arteriolosclerosis solely describes the affected vessel size (small arteries and arterioles), rather than its histopathologic appearance. (200) The thickening of the small arteries can occur throughout the body and is often related to hypertension and diabetes mellitus. A histological distinction is made between two subtypes: the hyperplastic type and the hyaline type. In hyperplastic arteriolosclerosis the arterioles get concentrically enclosed by thickened SMCs and fibrous deposits, resembling an “onion skin”. This leads to progressive narrowing of the lumina, ultimately resulting in necrosis. The hyperplastic subtype is typically affiliated to marked hypertension. On the contrary, hyaline arteriolosclerosis develops in cases of modest hypertension due to increased production of extracellular matrix by SMCs, which respond to chronic hemodynamic stress. As the remodeling process progresses, the arteriolar intima is increasingly built of fibromuscular tissue, resulting in a luminal narrowing with ischemia of subsequent tissues. Microangiopathy, as a common feature of advanced diabetes, is partly caused by these arteriolar changes. In this case, hyperglycemia triggered endothelial dysfunction is the prevailing cause. (198, 201)

3.3.2 Inflammatory vasculopathies

Vasculitis is defined as inflammation of blood vessel walls and can affect any vessel from arteries to veins independent of size or localization. Despite ongoing research, certain fields of vasculitides are still poorly understood. Many mechanisms regarding the etiology and pathogenesis of inflammatory processes within the blood vessel walls remain unsolved and need further investigation. In general, infectious vasculitides, which are caused by pathogens directly invading and proliferating within vessel walls, and noninfectious vasculitides are distinguished. The latter are commonly caused by autoimmune processes, while malignancy- and drug-induced vasculitides due to paraneoplastic and drug side effects also occur. To establish

specific definitions and appropriate names for the various entities, the “International Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Systemic Vasculitides” was initiated to unify the different terms of inflammatory vascular diseases. (202) The primary goal of the conference was to create a uniform nomenclature, but this also allows a categorization principally based on the size of the predominantly involved vessels defining large-, medium-, and small vessel vasculitis. Large vessels include the aorta and its major branches with analogous veins. Medium size vessels comprise the main visceral vessels and their initial branches, coronary and cutaneous vessels. Intraparenchymal vessels, arterioles, capillaries, and venules are considered small vessels. Despite this categorization, a key concept implies that vasculitides of all three major categories can affect every vessel size. Considerably is the fact that microorganisms can also indirectly impair the vascular walls without invading the vessel walls per se. (202, 203) Moreover, vascular involvement is also frequently observed in other systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, sarcoidosis or Sjögren´s syndrome. (204)

Therefore, the abovementioned classification of vasculitides was implemented to distinguish the various entities regarding their potential etiology and predominantly affected vessel size. As already stated, vasculitides are divided into infectious and noninfectious forms. A complicating factor in this categorization is increasing evidence, that many pathogens might be indirectly involved in the pathogenesis of vasculitis, especially via immunological effects. (205) Noninfectious vasculitis typically derives from autoimmune phenomenons leading to inflammation of vessels. Immune cells, pro-inflammatory cytokines and autoantibodies play a major role in their pathogenesis. The underlying causes triggering these autoimmune reactions are often unknown but multifactorial etiology with the interplay of genetical, environmental, infectious, and immunologic elements are considered responsible in many entities. Certain hypotheses on the probable etiology of classic autoimmune vasculitides, including Takayasu´s arteritis (TAK) are linked to microorganisms and infections. (204) The indirect immunological effects ensuing from pathogens include type II, III, or IV hypersensitivity reactions. (205) A steady causal relationship between infection and vasculitis, however, has only been established in chronic hepatitis B virus (HBV)-associated polyarteritis nodosa (PAN) and hepatitis C virus (HCV) with cryoglobulinemic vasculitis (CV). Both infection-associated forms rank

among the immune complex (IC) vasculitides, and thereby share the same pathogenesis as idiopathic CV. On the contrary, the etiology and pathogenesis of idiopathic PAN remains mainly concealed. Table 1 gives an overview of the classification of vasculitides of the CHCC and adds selected infection-associated and direct infectious vasculitides.

Table 1. Classification of Vasculitides according to Vessel Size and Etiology, adapted from the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (202)

Affected Vessel Size	Autoimmune Vasculitides	Infection Associated Forms	Infectious Vasculitides
Large Vessel Vasculitis:			
	Takayasu arteritis (TAK)	Tuberculosis associated TAK	Infective aortitis (IA)
	Giant cell arteritis (GCA)		Q fever/ Coxiella burnetii vasculitis
Medium Vessel Vasculitis:			
	Polyarteritis nodosa (PAN)	HBV associated PAN HIV - PAN-like	VZV - vasculitis
	Kawasaki disease (KD)	HIV - KD	Toxoplasma - retinal vasculitis
Small Vessel Vasculitis:			
ANCA-associated vasculitis:	Granulomatosis with polyangiitis (GPA)	CMV - vasculitis	Rickettsial vasculitis
	Eosinophilic granulomatosis with polyangiitis (EGPA)		PVB19 - (leukocytoclastic) vasculitis
	Microscopic polyangiitis (MPA)		
Immune Complex Vasculitis:	Anti-glomerular basement membrane disease		EBV - vasculitis
	Cryoglobulinemic vasculitis	HCV-Cryoglobulinemic vasculitis	
	IgA vasculitis		
	Hypocomplementemic urticarial vasculitis		
Single-Organ Vasculitis			
	Primary CNS vasculitis	HIV - CNS angiitis	

3.3.2.1 Direct and indirect infection-associated vasculitides

As depicted in table 1, many microorganisms can induce vasculitis by different pathophysiological ways leading to miscellaneous symptoms.

In HBV-PAN, inflammation of vascular walls is evoked by type III hypersensitivity reaction with immune complex depositions containing HBsAg, immunoglobulins and complement. Immune complex driven activation of the classic complement pathway and neutrophil recruitment resulting in the damage of endothelium and vessel wall summarizes the assumed process. The predominantly involved vessels include medium to small arteries, joining the ranks of medium vessel vasculitides. Onset of vasculitis usually begins within twelve months of acute HBV infection and is associated with both more severe courses and frequent involvement of nerves, heart, and the gastrointestinal system. In HBV-PAN, weight loss and fever are often accompanied by mononeuritis multiplex, arthralgias and myalgias. Patients developed malignant hypertension, cardiomyopathy, orchitis and ischemic abdominal pain more frequently compared to non-HBV related PAN cases. In total, PAN is a rare manifestation in HBV patients with a prevalence of less than 1%. Conversely, in patients with PAN defining disease patterns concomitant HBV infections are present in under 7% of cases. (204)

In the case of HCV-CV, virus associated cryoglobulins (type II or III) appear, also referred to as mixed cryoglobulinemia (MC). Following HCV infection, mono- and polyclonal IgM with rheumatoid factor (RF) activity are produced from chronically stimulated B-cell clones. By complex formation with polyclonal anti-HCV IgG antibodies, cryoglobulins arise. Besides IgM and IgG, these ICs contain viral antigens and HCV RNA and trigger the activation of the complement cascade via binding to C1q. C1q receptors on the surface of blood and endothelial cells in turn bind the complexes, promoting subsequent vascular inflammation with small vessel involvement. Characteristic manifestations of CV include cutaneous vasculitis, membranoproliferative glomerulonephritis, and peripheral neuropathy. Patients complain about purpura as one of the leading symptoms, as well as arthralgias, Raynaud´s phenomenon and hypertension. End-stage renal disease is infrequently observed in the case of renal involvement. Although MC is encountered in 40-70% of patients with HCV, symptomatic CV is prevalent in only 5% of this population. (204, 205)

Infectious aortitis (IA), a potential lethal disease if left untreated, is caused by various bacteria. *Staphylococcus aureus, Enterococcus sp.* and *Streptococcus pneumoniae*, as representatives of gram-positive cocci constitute the main pathogens in IA accounting for approximately 60% of cases. The enteric gram-negative bacterium *Salmonella* is another frequently detected organism in aortitis, among numerous others (including fungi e.g. *Candida* and *Aspergillus* species) described in the literature. *Treponema pallidum,* the pathogen of syphilitic aortitis, played a major role in the pre-antibiotic era but is still encountered nowadays in untreated tertiary syphilis. Additionally, also infections with *Mycobacterium tuberculosis* can lead to IA as a complication of active tuberculosis. Tuberculous aortitis typically manifests after hematogenous spread of bacteria, frequently triggering pseudoaneurysms. (206) IA typically affects older men with atherosclerosis, or patients suffering from congenital aortic anomalies. Patients with reduced immunocompetence due to diabetes, cancer and immunosuppressive therapy are also considered populations at risk. The pathogens invade the aortic wall via bacteremia, which often derives from infective endocarditis or a distant source of infection. Direct expansion of pathogens from adjacent tissue or contamination of the vascular wall after a trauma have also been described. The microorganisms can enter the vessel wall directly through the aortic adventitia or via embolization into the vasa vasorum. Both mechanisms lead to disruptions of supplying vessels and further inflammation and infiltration of the wall. Severe complications of infective aortitis are aortic (mycotic) aneurysms, rupture, aorto-duodenal fistula, and vertebral osteomyelitis. Prolonged fever with dorsal, thoracic, or abdominal pain is a common feature but asymptomatic cases with incidental findings of aneurysms on thoracic or abdominal images are also reported. (205, 207, 208) As syphilis-associated aortitis was implemented in the category “vasculitis associated with probable etiology” of the CHCC in 2012, it is introduced in more detail. Syphilitic aortitis commonly occurs 10 to 30 years after the primary infection and becomes clinically manifest in 10-15% of untreated syphilis cases. The long timeframe between infection and onset of symptoms makes diagnosis of syphilitic aortitis difficult. Nevertheless, it is a differential diagnosis important to consider, as lethality within one year is up to 80%, especially in the scenario of aneurysms. The destructive infiltration of the treponemes into the vasa vasorum and aortic adventitia results in perivascular lymphoplasmacytic inflammation. The devastating

consequences include adventitial scarring, obliterative endarteritis and medial necrosis of elastic fibers. These processes cause intimal thickening and wrinkling, leading to the typical “tree bark” appearance in syphilitic aortitis. Subsequent complications derive from the weakening of the vascular integrity, including the abovementioned aortic aneurysm, aortic root dilation and aortic valve insufficiency. Coronary ostial stenosis emerges from the aortic wall thickening following fibrosis of the media and formation of scar tissue. In view of diagnosing syphilitic aortitis, CT angiography (CTA) is the preferred imaging method, enabling the detection of aneurysmal dilatation, circumferential wall thickening and coronary ostial stenosis. (207)

Besides causing IA, preceding infections with the strictly aerobic, acid-fast bacterium *M. tuberculosis* have also been linked to TAK, partly because granulomatous lesions are characteristic in both diseases. Additionally, studies showed immune responses directed against heat-shock proteins of the mycobacterium, and these findings were corroborated by the detection of mycobacterial gene sequences within aortic tissue from patients with TAK (23 out of 33, 70%). Hence, this suggests a potential role of *M. tuberculosis* in inducing TAK, possibly via mycobacterial antigens mimicking vascular peptides, thereby triggering cross-reactivity. (209-211) As tuberculosis can affect nearly every part or organ of the body, also tuberculous vasculitides occur at various sites, affecting different vessel sizes. For example, *M. tuberculosis* can lead to tuberculous cerebral vasculitis, a complication of tuberculous meningitis. Affected patients suffer from motor deficits, acute confusional states, headaches, convulsions, or meningeal syndrome, and brain infarctions commonly occur. (212) Tubercular retinal vasculitis is another manifestation frequently diagnosed in patients with ocular tuberculosis. (213) Diagnosis is based upon characteristic signs and symptoms together with a diligent clinical examination and imaging procedures, including brain CT and magnetic resonance imaging (MRI) as well as fundoscopy, respectively. Skin involvement with cutaneous leukocytoclastic vasculitis further illustrates the diverse vasculitic syndromes associated with tuberculosis and its potential to affect vessels of all sizes. (214)

Arthropod-borne infections can also affect the vessels, with Rickettsiae showing special tropism to endothelial cells. Different species of the gram-negative, obligate intracellular bacteria are causing vasculitides, especially *Rickettsia rickettsii* (Rocky

Mountain spotted fever, RMSF), *Rickettsia conorii* (boutonneuse fever) and *Rickettsia prowazekii* (epidemic typhus). After skin inoculation, the pathogen spreads through lymphatics into the vascular system, where it infects and replicates in microvascular endothelial cells. The result is a benign maculopapular rash as a common feature of infection. In untreated cases, the infection may progress with invasion of small arteries and veins, leading to a systemic small vessel vasculitis. Small vessels of the brain, lungs and kidneys are mostly affected, causing edema, hypotension and multiorgan failure due to an increase in vascular permeability. In RMSF, typical symptoms occur after an incubation period of 2-14 days with headache, nausea with or without vomiting, myalgias, fever, and abdominal pain. The characteristic rash appears after three to five days, and an eschar may be apparent upon careful history taking and physical examination. Real-time PCR of skin-biopsy specimens is the diagnostic analysis of choice, providing adequate sensitivity and prompt diagnosis. (205, 215-217) Further intracellular pathogens causing infrequently vasculitis are *Ehrlichia chaffeensis* and *Coxiella burnetii*. (205)
Besides bacterial, viral, and fungal infections, also parasites can trigger vasculitis or directly invade vessel walls. A known representative is the protozoan parasite *Toxoplasma gondii,* the causative agent of ocular toxoplasmosis. The typical manifestations of ocular toxoplasmosis include recurrent posterior uveitis with unilateral, necrotizing retinitis and secondary choroiditis. Patients often complain about floaters, sometimes in conjunction with altered vision. These findings are usually seen adjacent to a pigmented retinochoroidal scar and associated with retinal vasculitis. If retinal vasculitis is present, the local venous vasculature is more often involved than the retinal arteries (medium arteries). Segmental arteriolitis is another suggestive feature of the disease, known as Kyrieleis arteriolitis or plaques. The diagnosis is typically established by the characteristic clinical presentation but might be confirmed with DNA PCR or specific antibody detection in ocular fluid. (205, 218)
Aside from HBV and HCV, numerous other viruses have been linked to either direct or indirect vascular injury and inflammation. With ongoing research on vasculitic syndromes, the pathomechanisms of viral infections may be further enlightened to uncover their true impact on vasculitides.
In patients with HIV infection, vascular inflammation is a frequently observed complication. Different mechanisms for the induction of vasculitis are proposed with

an interaction of various hypotheses as the probable actual cause. Injury of vessel walls might occur by direct viral replication within the vascular tissue. Lymphocytic overactivity and elevated levels of inflammatory cytokines emphasize a persistent immune activation. In combination with depositions of ICs in the vessel walls or formation on-site, they represent further potential pathophysiological pathways. Additionally, HIV infections promote the susceptibility to opportunistic infections (*T. gondii*, *Pneumocystis jirovecii*), co-infections (HBV, HCV, CMV) and hypersensitivity to antiviral drugs and hereby indirectly trigger vasculitides. (204, 216) HIV-associated vasculitides differ in affected vessel size, ranging from large to small vessel vasculitis, and their histological appearance, which resembles giant-cell arteritis or necrotizing vasculitis. (215, 219) The most common vasculitic syndrome found in HIV patients is that of a PAN-like medium vessel vasculitis. In contrast to idiopathic PAN, it is more focal and unlikely to take a fulminant course. HIV-PAN typically involves the neuromuscular system and skin. (204, 215, 216) Angiitis of the central nervous system (CNS) in the setting of HIV infection is another common entity with heterologous etiologies. The causes encompass direct HIV vasculitis, co-pathogen infection or angiocentric lymphoproliferative lesions. To aggravate diagnosis, cerebral vasculitis can also develop after initiation of highly active antiretroviral therapy. This results in an overwhelming immune response to subclinical, often opportunistic infections, called immune reconstitution inflammatory syndrome. (215) Kawasaki disease (KD), known to be linked with preceding bacterial or viral infections especially in children, is also found in adult HIV patients. Approximately one-third of reported adult KD cases are related to HIV infections with clinical appearance and therapy not deviating from other KD manifestations. (204)

Parvovirus B19 (PVB19) is a small, non-enveloped DNA virus and pathogen of erythema infectiosum (“the fifth disease”) especially in children. PVB19 possesses tropism for many different cells, including erythroid progenitors but also endothelial cells. The main receptors for viral attachment and entry into the cells represent the P blood group antigen globoside and α5β1 integrins. Thereby, it is assumed that the virus invades endothelial cells leading to vascular inflammation. Parvovirus has been linked to the pathogenesis of several autoimmune vasculitides, including PAN, granulomatosis with polyangiitis or giant cell arteritis (GCA), however comprehensive studies failed to detect conclusive connections. (204, 215) In cases

of proven PVB19 vasculitides, small vessels were affected in the majority, showing a leukocytoclastic pattern in afflicted organs (skin, kidneys). (204) In a case study of 49 adults infected with PVB19, 18% had skin lesions with palpable purpura. Histology confirmed cutaneous vasculitis displaying superficial perivascular inflammation and leukocytoclasis. (220) Diagnosis is built upon detection of specific IgM antibodies and corroborated by positive PCR for viral DNA in skin lesions or serum. (204)

Cytomegalovirus (CMV) affects patients irrespective of their immune resistance, albeit immunocompromised hosts are infected more often and tend to run severe, disseminated courses. Patients may present with clinical signs coinciding with small to medium-sized vessel vasculitis, demonstrating the viral capability to infect endothelium. (215) Besides direct vascular damage, viral antigens expressed by afflicted cells activate host immune responses against these cells, resulting in inflammation. (216) Histopathologic workup of biopsies from affected organs reveal leukocytoclastic or granulomatous vasculitis. (204) CMV vasculitis typically involves the gastrointestinal tract, especially the large bowel. Gastrointestinal vasculitis may be present with abdominal pain and febrile diarrhea due to ischemia, perforation, and hemorrhage in more severe courses. In addition, retinal or skin manifestations are described and neurologic deficits due to CNS or peripheral nervous system infarcts occur as well. (205, 215) CNS vasculitis appears in the form of encephalopathy, meningoencephalitis, cranial nerve palsy or radiculopathy. Skin lesions often refer to disseminated and therefore menacing infections, with a higher risk of fulminant progression. (216) Manifestations within the skin range from purpuric lesions, to subcutaneous nodules to vesicles or erythematous rashes. (217) CMV vasculitis is diagnosed based on biopsy specimens with identification of cytomegalic endothelia and characteristic intranuclear inclusion bodies in macrophages. This is complemented by the detection of specific antigens and/or detection of CMV DNA. (204, 205)

Infections with the varizella zoster virus (VZV) can lead to direct viral invasion of the vessel walls with subsequent inflammation. The most common feature of VZV-vasculitis is granulomatous CNS vasculitis, which affects large and small cerebral vessels. It has been observed in primary infections (varicella) as well as reactivations of the virus (zoster). The duration from primary infection to the clinical manifestation of CNS vasculitis is approximately four weeks. In contrast, cerebral

vasculopathy following zoster ophthalmicus or any other zoster location may emerge up to two years thereafter. Of note, more than one third of patients did not suffer from typical rash, with some solely complaining about herpetic neuralgia. Symptoms of CNS vasculitis can reflect both unifocal or multifocal disease presentations, covering acute hemiplegia, transient ischemic attack (TIA), and other stroke syndromes, as well as rapidly progressive multi-infarct dementia or intranuclear ophthalmoplegia. Concurrent VZV myelitis and meningitis are frequently observed. VZV associated retinal vasculitis, as a variant of CNS vasculopathy, is one of the most common causes of acute retinal necrosis syndrome. (205, 215) However, vascular inflammation is not limited to cerebral and ocular sites but has also been reported to affect the skin and kidney. (216) Yet again, VZV vasculitides occur in both immunocompetent and immunosuppressed individuals with a higher risk of aggravation and severe courses in the latter. Histopathologic features of impaired vessels show segmental inflammatory infiltrations by lymphocytes or histiocytes, sometimes with fibrinoid necrosis or multinucleated giant cells (granulomas). (221) Diagnosis of CNS vasculitis is supported by MRI revealing ischemic or hemorrhagic infarctions, characteristically within grey-white matter junctions. Additionally, segmental narrowing with large- and small-vessel involvement is diagnosed, often accompanied by post-stenotic dilatation as seen on angiography. While VZV DNA is detected in only one-third of cerebrospinal fluid (CSF) samples, specific anti-VZV IgG antibodies are found in 93% of cases with lymphocytic pleocytosis as another common feature (67%). (204) Several other pathogen-associated vasculitides have been described in the literature and gain of knowledge will further increase their quantity. Additional viruses worth to be mentioned include Epstein-Barr virus (EBV), capable of provoking IC vasculitis involving small vessels and renal glomeruli or leukocytoclastic vasculitis. The herpes simplex viruses 1 and 2 may also infect small to medium size arteries, leading to cutaneous, retinal, or necrotizing vasculitis and the onco-retrovirus human T lymphotropic virus type 1 is also known to trigger vascular lesions directly, or indirectly. (205)

3.3.2.2 Noninfectious vasculitides

As mentioned in the introduction chapter to vasculitides (3.3.2), the specific etiology and pathomechanisms of noninfectious vasculitides are frequently unknown, but autoimmune responses are predominantly involved. Therefore, the main autoimmune-mediated vasculitides are described, including TAK, GCA, PAN, KD, and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV). Immune complex formation with vascular deposition, like ANCA, and pathogenic T lymphocyte responses rank among the major autoimmune phenomenons observed in these diseases. (222) Overall, primary vasculitides are rare conditions, however, fundamental epidemiologic differences arise among different age groups, race, and gender. A female predominance is seen in both large vessel vasculitides, TAK and GCA, whereas PAN and AAV occur more frequently in males. (223) Moreover, while TAK is more prevalent in Northeast Asia, typically affecting women between 15 to 40 years of age, GCA exhibits the highest incidence in Scandinavia, typically observed in people aged ≥50 years. The medium vessel vasculitis PAN, as well as the small vessel affecting AAVs have a mean age of onset between 40 to 60 years. (223, 224) Compared to the other vasculitic syndromes, the medium vessel vasculitis KD predominantly affects children below the age of five, with peak incidences among individuals from East Asian descent. (224) Table 1 outlines autoimmune vasculitides with their predominantly affected vessel sizes. Common constitutional symptoms, indicating systemic inflammation in autoimmune vasculitis, comprise fever, weight loss, anorexia, malaise, fatigue, night sweats, headache, myalgias, and arthralgias.

3.3.2.2.1 Takayasu arteritis (TAK)

TAK typically affects the aorta and the proximal segments of its major branches, and pulmonary artery involvement frequently occurs. The exact etiology of TAK is unknown but immunopathogenic mechanisms and associations with the human leukocyte antigen (HLA)-B*52 are suspected. Histopathologic studies reveal a T cell-mediated, granulomatous panarteritis with inflammatory mononuclear cell infiltrates and occasionally giant cells, primarily situated in the media and adventitia. (203, 222, 225) Inflammatory processes lead to intimal proliferation and fibrosis, in combination with disruption and degeneration of the elastic lamina, as well as a scarred media. This results in a decrease in the vascular lumen and characteristic

symptoms due to the compromised blood flow occur in the supplied organs. Pulselessness of affected vessels is a typical feature of TAK. As the subclavian artery is commonly involved, ischemic symptoms of the upper limb frequently occur. Additionally, affections of the common carotid arteries and abdominal aorta manifest as visual changes (amaurosis, diplopia), syncope, TIA, or stroke, and abdominal pain, nausea, or vomiting, respectively. Arterial hypertension might express renal artery involvement. Laboratory studies characteristically reveal mild anemia with ESR and immunoglobulin level elevations. (222)

3.3.2.2.2 Giant cell arteritis (GCA)

Although GCA resembles TAK in regard of the affected vessels (aorta and its major branches), it commonly presents with cranial artery involvement. While approximately 30% of patients solely suffer from temporal arteritis, concurrent symptoms of polymyalgia rheumatica occur in 40-50% of GCA cases. (203, 222) Similar to TAK, the etiology of GCA is unknown but associations with genetic factors were found, especially for HLA-DRB*04 alleles. In view of pathogenetic and histopathologic features, GCA also shows panarteritis in the form of a granulomatous inflammation, but giant cell formation is more frequent than in TAK. Dendritic cell activation, followed by cytokine production and release via T helper 1 and 17 cells orchestrate the pathogenesis of GCA, resulting in vascular remodeling with ischemia of downstream organs and tissues. Patients with the characteristic cranial artery involvement suffer from headache, often accompanied by a tender, thickened, or nodular artery. Claudication of the jaw and tongue, especially while chewing, and scalp pain are further characteristics. In this scenario, ischemic optic neuropathy constitutes the most severe complication, resulting in irreversible visual loss unless treated in time. Precursors may include diplopia, amaurosis fugax, or visual blurring. (222, 225) Laboratory findings include markedly elevated ESR, increased CRP, normochromic anemia, and thrombocytosis. (203)

3.3.2.2.3 Polyarteritis nodosa (PAN)

The medium and small muscular arteries affecting PAN is defined as a necrotizing arteritis, in which glomerulonephritis, ANCAs, and granulomas are absent, and arterioles, capillaries, and venules are not involved. (202) PAN lesions typically show a segmental affection pattern, with bifurcations and branchings of arteries as predilection sites. While specific infection-associated forms are common (HBV-

PAN, chapter 3.3.2.1) and arise with immune complex depositions, in the majority of cases the etiology remains elusive. Histopathological samples uncover polymorphonuclear neutrophils, which infiltrate the entire vascular wall and perivascular areas during the acute stages. With progression of the disease, mononuclear cells infiltrate the lesions and the vascular reactions of intimal proliferation and degeneration of the wall proceed to fibrinoid necrosis. Luminal narrowing with subsequent thrombosis, infarction of supplied tissues, and hemorrhage are the consequences. Another typical finding in PAN is aneurysmal dilatation that are particularly found in the commonly affected renal and visceral vessels. Their involvement also explains the characteristic symptoms of PAN, comprising arterial hypertension, renal insufficiency, or renal infarction, and emesis, diarrhea, or intestinal bleeding in the case of visceral involvement. Additional clinical manifestations involve the skin (e.g. rash, purpura, nodules) and the nervous system (peripheral neuropathy, mononeuritis multiplex). Laboratory studies commonly reveal leukocytosis and anemia of chronic disease, coupled with elevated CRP and ESR values. (203, 222)

3.3.2.2.4 Kawasaki disease (KD)

Ranking among the most common vasculitides in childhood, the systemic inflammatory disease KD predominantly affects small and medium arteries. (202) Different hypotheses have been proposed regarding the etiology of KD, with the combination of genetic predisposition and infectious triggers as the most promising. (226, 227) Following the onset of disease, infiltration of inflammatory cells, including neutrophils, lymphocytes (CD8+ T cells), and macrophages, into the vascular tissue ensues, which is especially profound in the coronary arteries. The resulting vascular damage concerns endothelial cells, the elastic lamina, and medial smooth muscle cells with intimal proliferation seen in pathologic studies. Due to the decay of elastic and collagen fibers, along with disruptions of the vascular integrity, beadlike aneurysms and thromboses might develop. (222, 228) Persistent, pronounced fever with bilateral conjunctivitis, cervical adenitis, polymorphous exanthema, erythema of lips and oral mucosa, as well as palms and soles define the clinical hallmarks of KD. Laboratory manifestations include elevated levels of CRP and ESR, leukocytosis and anemia (normochromic and normocytic), as well as thrombocytosis one week after symptom onset. The aforementioned aneurysms play a key role in

long-term sequelae of KD, as coronary artery aneurysms and thromboses can result in myocardial infarction years after disease onset. (225, 229)

3.3.2.2.5 ANCA-associated vasculitides (AAV)

Alongside the predominance of small vessel involvement, the characteristics of this group of vasculitides are the frequently present antibodies directed against specific proteins within cytoplasmic granules of neutrophils and monocytes, called ANCA. Two main ANCA targets allow the categorization into cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA). This terminology refers to the distinct staining patterns, seen in immunofluorescence microscopy, when sera of AAV patients are added to ethanol-fixed indicator neutrophils. AAV contain three distinct vasculitic syndromes: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). Over 90% of patients with active GPA feature a cANCA pattern, with antibodies directed against their major antigen proteinase-3. pANCA in contrast, which are primarily directed against myeloperoxidase (MPO), are seen to a lower extent in EGPA and MPA. However, the exact role of ANCA in AAV pathogenesis and progression is unclear and subject of ongoing debates. (222) Again, the etiology of AAV remains elusive but a combination of genetic and environmental triggers is discussed. (230)

3.3.2.2.5.1 Granulomatosis with polyangiitis (GPA)

Small vessels of the upper and lower respiratory tract and kidneys are typically affected in GPA. Histopathologically, necrotizing vasculitis with multinucleated giant cell granulomas are characteristic findings. In the case of renal involvement, focal and segmental necrotizing glomerulitis might be seen, potentially resulting in a rapidly progressive crescentic glomerulonephritis. Patients with upper respiratory tract involvement frequently suffer from sinusitis and otitis media, as well as nasal disorders. In the latter, purulent or bloody discharge, mucosal ulceration, and septal perforation, which might lead to saddle nose deformity, comprise common findings. Additionally, cough, hemoptysis, and dyspnea can reflect the pulmonary infiltrates and nodules, which are commonly detected by imaging techniques. Symptoms indicative of glomerulonephritis often prevail, with proteinuria, hematuria, and erythrocyte casts. (203, 222)

3.3.2.2.5.2 Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is characterized by a necrotizing, granulomatous angiitis predominantly of small vessels with the typical development of extravascular granulomas. It is accompanied by asthma and peripheral and tissue eosinophilia. Multiple organ systems might be involved, but pulmonary findings dominate the clinical picture with patients complaining about asthmatic disorders such as rhinosinusitis and aggravating severe asthmatic attacks. The commonly observed skin lesions (purpura, nodules), mononeuritis multiplex, and mild renal disease demonstrate the systemic effects of EGPA. (203, 222)

3.3.2.2.5.3 Microscopic polyangiitis (MPA)

MPA leads to necrotizing vasculitis primarily of small vessels and differs from GPA and EGPA due to the absence of granuloma formation. Frequently involved organs are the kidneys and lungs, with glomerulonephritis and pulmonary capillaritis as very common features. Histological specimens of MPA patients lack immune-complex formation and resemble GPA in the case of renal lesions. Similar to GPA, MPA often triggers glomerulonephritis and pulmonary disorders, with hemoptysis, and dyspnea as initial symptoms. Additional symptoms include mononeuritis multiplex, gastrointestinal complaints, and purpura. (203, 222)

3.3.3 Complications of vasculopathies

Despite their miscellaneous pathomechanisms and etiologies, many of the abovementioned diseases trigger similar complications over time. The combination of remodeling processes of the vascular walls, which lead to luminal narrowing and stenosis, and the local pro-inflammatory milieu markedly increases the risk of thromboembolic events. Therefore, arterial and venous thromboembolic events constitute major complications of vasculopathies and are described in more detail.

3.3.3.1 Thrombosis and Embolism

Thrombosis defines the process of intravascular, intravital coagulation of blood leading to the obstruction of blood vessels. Depending on the formation mechanism, different composition types of thrombi are distinguished with precipitation, stagnation and hyaline thrombi ranking among the most important. Pathological formation of blood clots typically arises from three major factors, which often occur combined. Endothelial dysfunction as one factor originates from structural or

functional changes of the endothelium or basal membrane. Especially injuries of the endothelium caused by atherosclerosis, hypertension or trauma are of great relevance. Exogenous substances, immunological reactions and inflammatory processes can also disrupt the endothelial integrity and thereby promote thrombogenesis. Disorders of the hemodynamics, predominantly stasis of the blood flow, represent the most relevant causes of coagulation in expanded veins, aneurysms and dilated left atriums. Right heart failure slows the venous return from the periphery, especially from the veins of the legs triggering deep vein thrombosis, which in turn is the most common origin of PE. The aggregation of activated clotting factors and thrombocytes yields thrombus formation. Changes in blood composition such as higher cell counts, or volume deficiencies result in more viscous blood with greater flow resistance. Therefore, these changes lead to a hypercoagulable state. Taken together, these factors constitute the Virchow´s triad. The pathogenesis of the different thrombus types is closely related to the aforementioned factors. The development of precipitation thrombi is based on endothelial activation or injury with the exposure of subendothelial structures, initiating the adhesion of thrombocytes to the vessel walls. Downstream of this process, fibrin covers the formed platelet thrombus to form a network and erythrocytes and leukocytes attach. Precipitation thrombi are preferably observed in regions of atherosclerotic plaques and vasculitides and represent the predominant type of arterial thrombi. Stagnation thrombi in contrast develop from stagnating blood within the vessels. Activated clotting factors, platelets and endothelial cells lead to fibrin deposits with clotting of the entire blood column. The result is a complete obstruction of the affected blood vessel. In general, stagnation thrombi are encountered in the venous vascular system due to a delayed blood return. Hyaline thrombi typically form in venules, capillaries and less common arterioles in patients suffering from disseminated intravascular coagulation (DIC). (199, 222)

One of the feared complications of thromboses is embolism. Emboli are specified as corpuscular materials, which occur when thrombi detach and travel via the bloodstream to other regions of the vascular system, until they lodge and obstruct another vessel. Apart from thrombi, which are the most frequent cause of emboli, also fat, cholesterol, cells, amniotic fluid, and foreign bodies may lead to embolism. The distinction between venous, arterial, and paradoxical emboli is determined by the origin of the thrombus. PE marks the most abundant venous thromboembolism,

which can originate from thrombosis of the deep and superficial veins. In comparison, 80% of arterial thromboembolic events arise from the left heart and can therefore impact any of the downstream arterial vessels. Paradoxical thromboemboli are rare and only observed in individuals with a patent foramen ovale or septal defects, where emboli directly cross from the right to the left heart. (199, 222)

3.3.3.1.1 Venous thrombosis and thromboembolism

The term venous thromboembolism comprises vein thrombosis and PE and is associated with acute pulmonary and cardiovascular complications and sequelae. Long term effects declining the quality of life include postthrombotic syndrome or chronic venous insufficiency and chronic thromboembolic pulmonary hypertension with the development of edemas of calf and ankle, leg aching or ulcers and breathlessness with reduced physical resilience, respectively. (222)

3.3.3.1.1.1 Superficial and deep vein thrombosis

The acute or chronic obstruction of deep veins is defined as DVT, which may progress into proximal or distal parts of the vessel. In contrast, superficial vein thrombosis (SVT) refers to thrombosis of superficial veins, predominantly of the lower extremity, which include the great, accessory, and small saphenous veins. Of note, both venous thrombotic diseases may lead to VTE. (231) Epidemiological data suggest an incidence of DVT of one to two cases per 1000 inhabitants per year and rates rise with age. (232) Although less studies are available regarding the epidemiology of SVT, data presume higher incidence rates compared to DVT. (233, 234) On the basis of the Virchow´s triad, different factors facilitate the formation of venous thrombosis. The common predisposing factors include surgery, traumata, heart failure, malignancies, obesity, pregnancy, therapy with sexual hormones and any kind of immobilization in general, including being bedridden. In addition, genetic prothrombotic states promote blood clotting, with the gene mutations of factor V Leiden and prothrombin being the most common causes of thrombotic events. Inflammatory processes and infections promote thromboses via enhancing the coagulation activity, and psoriasis and inflammatory bowel disease gained recognition as further VTE risk factors. However, in about one third of VTE cases the cause remains unknown. One typical pathogenetic mechanism of DVT is venous stasis by loss of the muscular pump function in immobilized patients. This leads to

a doubled event rate in long-term bedridden states compared to transient periods. Of clinical importance is the fact that 20% of patients with spontaneous and apparently unprovoked VTE suffer from tumor disease. Further diagnostics to rule out potential malignancies are always indicated in this patient population. (203, 222, 232) For SVT, additional significant risk factors are varicose veins and their excision or ablation procedures, as these impaired veins account for almost 90% of cases. (231, 235) The most common symptoms in DVT are cramps and pain in muscles, especially in the lower calf, which commonly endure and worsen over several days. Swelling, pain and cyanosis of the affected leg are the considered characteristic triad of symptoms, although they are unspecific and only occur in about 50% of cases. Typical signs and symptoms of SVT include the cardinal signs of inflammation, with tenderness, induration, pain, and erythema along the course of the affected vein. On clinical examination, the thrombus might be palpable as a hardened or nodular cord. In cases of high fever, suppurative SVT must be excluded. Moreover, SVT often progresses to DVT, and in patients also complaining about DVT symptoms, evaluation of concurrent thromboembolism is indicated. Despite these typical symptoms, the clinical diagnosis of SVT is confirmed by duplex and compression ultrasonography to visualize the extent of thrombosis and to exclude a potential coexisting DVT. (231)

The routine diagnostics of patients with suspected DVT comprises the integration of the Wells-score to assess the pre-test probability. The likelihood of thrombosis is high if the two-step Wells-score is ≥ 2 points. In settings of high clinical probability, D-dimer testing can be omitted, and patients need to undergo compression ultrasonography and Doppler imaging. In other cases, D-dimer testing may rule out VTE, if values are within normal range, making further diagnostics unnecessary. However, if the result is positive, additional imaging is indicated. (232) When thrombi are visible during ultrasonography, their ends should be identified to assess the proximal and distal expansion. In patients with diagnosed DVT, evaluation of blood count and coagulation parameters is obligate. At the same time, further investigations should be initiated to detect the causative agent of the DVT. A diligent and targeted diagnostic approach followed by immediate therapeutic interventions can efficiently reduce the risk of complications and sequelae. Aside from PE, phlegmasia cerulea dolens is another complication and related to significant morbidity and mortality. It occurs in about 3% of DVT cases and presents with

severe pain in the leg, an extensive bulging edema and cyanosis of the affected extremity. Phlegmasia cerulea dolens is the result of severe thrombus progression, with obstruction of almost every vein of the leg and consequently rising tissue pressure with the compression of arteries. To avoid complications, prompt initiation of therapy including vascular compression therapy and adequate anticoagulation is important. Compression stockings with pressures of 30 to 40 mmHg relieve the swelling and pain and improve the venous return from the periphery through collaterals. However, the most important aspect is the effective prevention of postthrombotic syndromes, if prescribed and diligently worn at an early stage. Compression treatment should be continued for at least three months. In the case of SVT, compression therapy in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) constitutes the basic management. While initial anticoagulative therapy is mandatory in patients with DVT, it is only implemented in SVT patients who experience an elevated risk for VTE. (231) Initial anticoagulation in DVT is predominantly based on therapeutic doses of parenteral LMWH or fondaparinux for five to ten days followed oral anticoagulation. Unfractionated heparin (UFH) may be used in patients with severe renal insufficiency. Vitamin K antagonists are added and serve as the continuation therapy following initial anticoagulation. Another treatment option is the administration of direct oral anticoagulants (DOACs) with rivaroxaban and apixaban being suitable for both, initial and continuation therapy as monotherapies. In the case of prescription of edoxaban or dabigatran, five days of initial heparinization is indicated. Following the acute phase, the maintenance treatment is continued with either vitamin K antagonists or DOACs, in selected patients the heparin regimen might be continued. Depending on the individual benefit-risk profile, the anticoagulation therapy is continued for three to six months, in selected cases also long-lasting with annual risk-benefit assessments. Special indications may warrant pharmaco-mechanical therapy as well as venous thrombectomy and vena cava filters. (203, 222, 232)

3.3.3.1.1.2 Pulmonary Embolism (PE)

Acute PE, as a life threating complication of DVT, is characterized by partial or total obturation of pulmonary arterial vessels. PE can affect every blood vessel size, ranging from the main pulmonary arteries to the segment and subsegment pulmonary arteries. While epidemiological data suggest an increasing incidence of PE, the overall mortality seems to decline over the past years. Advances in

diagnostic techniques and further development of therapeutic approaches including oral anticoagulants contribute to this reduction. (236, 237) PE is the third leading cause for in-hospital death and about 20% of patients die before diagnosis or soon thereafter. Up to 90% of lethal PE occur in the first two hours after onset of symptoms. In general, the risk of suffering from PE doubles beyond the age of 40. (238) The primary cause of PE is thrombosis of the inferior vena cava or DVT of the lower extremities accounting for approximately 70 to 90% of all cases, whereby the risk of symptomatic disease is equal for partial and complete obstructing thrombi. After deep venous thrombi detach, they embolize to the inferior or superior vena cava followed by the right atrium and ventricle to the pulmonary arterial circulation, where they lodge and thereby cause acute PE. As a result, one of the main pathophysiological aspects is the alteration of hemodynamics, leading to a disparity between lung perfusion and ventilation, because affected lung areas may still be ventilated, but not perfused anymore. Sudden obstruction of at least 25% of the entire pulmonary arterial vessel cross-section is accompanied by an increase of the mean pulmonary artery pressure and a concomitant decrease of right ventricular ejection fraction (EF). Cardio-pulmonary failure is observed in prior cardiovascular healthy individuals with obstructions beyond 75%. With declining of the pulmonary perfusion, also the gas exchange surface diminishes, resulting in impaired oxygenation and arterial hypoxemia with compensatory hyperventilation and consecutive hypocapnia. Despite the reduced blood flow in involved lung areas, lung infarction only occurs in 10% of PE cases, partly because of additional oxygenated blood supply through bronchial arteries. If pulmonary infarctions occur, they are usually indicative of small, peripheral PE and provoke eminent pain, because of their proximity to pleural innervations. PE is classified upon severity, depending on size and site of the afflicted lung area. Massive PE affects half of the pulmonary vasculature and accounts for 5% to 10% of cases. It leads to hemodynamic instability and often presents as cardiogenic shock or multisystem organ failure, constituting high-risk PE. Submassive PE represents 20% to 25% of cases and is usually associated with right ventricular dysfunction, or elevated cardiac troponin levels but steady systemic arterial pressure. This category is also referred to as intermediate-risk PE. Most patients suffer from low-risk PE, which constitutes 65% to 75% of all PE, and is associated with an excellent prognosis. (222, 238)

Signs and symptoms of acute PE are versatile and nonspecific, making clinical diagnosis difficult. Furthermore, the severity of complained symptoms does not necessarily correlate with disease extent. While sudden onset of unexplained breathlessness is the most frequently stated complaint, additional symptoms such as retrosternal pain, coughing, tachycardia or hemoptysis are also common features. In cases of severe PE, patients can suffer from dizziness or syncope due to hypotension and shock. Concomitant signs of DVT might be encountered, but in many cases no signs of thrombosis are detected, as the embolization of the clot has already occurred.

A fast approach to the correct diagnosis of PE followed by appropriate therapy is critical to ensure high survival rates, because mortality peaks within the first 48 hours. Basic diagnostics are introduced to every patient with suspected PE to differentiate between hemodynamically stable or unstable states. The first diagnostical steps encompass a structured medical history, clinical examination, evaluation of vital signs, chest x-ray, an electrocardiogram (ECG) and blood gas analysis. (232) Early determination of the PE pre-test probability via Wells- or Geneva-score is indicated and influences the further diagnostic process. Similar to the evaluation of DVT, patients with low pre-test values should undergo D-dimer testing, while cases with a high likelihood are directly subjected to imaging tests. D-dimer values >500 µg/L are considered pathologic in patients younger than 50 years. Beyond the age of 50, the following formula is used to attune the D-dimer threshold to age: 10 µg/L * age of the patient. Additional diagnostics may reveal diminished oxygen saturation together with reduced PaO_2, indicating arterial hypoxemia, while lactate and partial pressure of carbon dioxide might be elevated in the blood gas analyses. Sinus tachycardia, P-pulmonale, T inversions in the right precordial leads (V_1-V_4) as well as complete or incomplete right bundle branch block are indicative signs of PE in the ECG. Another typical abnormality in ECG detected in about 20% of cases is the so called S1Q3T3 pattern, showing S waves in lead I, and Q waves and inverted Ts in lead III. Even though a chest x-ray is often inconspicuous in PE, it is still implemented to rule out differential diagnoses such as pulmonary edema, pneumonia, pneumothorax, or pleural effusions. (238) However, the imaging method of choice in the diagnostic algorithm represents a multislice-CT-pulmonary angiography for all patients who either show elevated D-dimer levels or a high pre-test probability. Optimized protocols with the highest possible contrast

lead to sensitivity and specificity of up to 96% to detect PE. The clinical examination and investigation of vital parameters is also pivotal to assess the hemodynamical situation of the patient and to distinguish stable patients from patients with unstable hemodynamics and potential signs of shock. Hence, the further course also depends on the received parameters and the hemodynamical state of the patient. After confirmation of acute PE in stable patients, a risk stratification should be conducted using the “pulmonary embolism severity index” (PESI) to determine both the 30-day risk of mortality and the preferred treatment. (239) Hemodynamically stable patients are categorized as non-high-risk patients with a 30-day risk of mortality ranging from 1 to 25%. Further discrimination between intermediate-low and intermediate-high PESI patients, include additional results from transthoracic echocardiography and cardiac biomarkers (Troponins and NT-pro-brain natriuretic peptide [NT-proBNP]). Echocardiography is performed to attest right ventricular dysfunction, while increased cardiac markers are indicative of a higher complication and mortality rate. In contrast, instable patients should immediately receive CTA if applicable. As an alternative, the evidence of right ventricular stress or pulmonary hypertension objectified by transthoracic echocardiography suffices to initiate reperfusion therapy, without further imaging procedures.

The basic care of acute PE cases includes upper body elevation and administration of oxygen. Depending on the blood gas analysis and the extent of tachypnea, intubation and mechanical ventilation might be indicated in possibly coexisting lung edema. Prompt administration of intravenous UFH with the opportunity to switch to a subcutaneous administration of LMWH, fondaparinux or the application of DOACs, if no reperfusion therapy is necessary, is essential within the first hours of therapy. Administration of heparins or fondaparinux should be maintained for at least five days. In cases of hemodynamically unstable conditions urgent revascularizing procedures are indicated. (240) Systemic thrombolysis to dissolve the obstructing pulmonary embolus with recombinant tissue plasminogen activator (rtPA) serving as the preferred intravenous fibrinolytic regimen is often initiated. Another option and back-up procedure is pharmaco-mechanical catheter-directed therapy, which commonly combines low-dose thrombolysis with physical fragmentation of the thrombus. Additional approaches include surgical interventions like pulmonary embolectomy. In all patients suffering from PE with preserved hemodynamics, oral anticoagulants are prioritized in the therapeutic process. The same principles

regarding the treatment regimens and pharmaceuticals in the therapy of DVT also apply to PE. Only cases categorized in the intermediate-high risk stadium should be kept under observation in the ICU for three days. If cardiac decompensation occurs, systemic fibrinolysis is also indicated in this patient population. (203, 222)

3.3.3.1.1.3 Cerebral venous thrombosis (CVT)

Another venous thrombotic disease, but less frequent compared to DVT, is CVT. The term commonly describes thrombotic occlusions of the dural sinuses as well as cortical vein thromboses, which often appear combined. (241) Studies estimated incidence rates of about 1.3 per 100,000 person-years in adults, with the highest rate in the age group between 31 to 50 years. Especially women of this group are at the greatest risk with 2.8 cases per 100,000 person-years. (242, 243) In comparison, CVT is rare in the elderly beyond the age of 65, who account for less than 10% of cases. (244) Conditions associated with the occurrence of CVT partly overlap with the risk factors for VTE. However certain risk factors are unique for this entity. Women, especially in the reproductive age and with the use of oral contraceptives, have a threefold risk for CVT compared to men. (245, 246) Additional CVT-specific risks include local infections (e.g. meningitis, mastoiditis or otitis), craniocerebral trauma, neurosurgical procedures or lumbar puncture. Still, intake of oral contraceptives is the most common acquired risk factor for CVT. (241, 247, 248) From a pathophysiological perspective, the two main subtypes of CVT entail distinct signs and symptoms. Cortical vein occlusion can lead to heightened venous and capillary pressure alongside disruptions in the blood-brain-barrier. Consequently, localized cerebral edemas arise, potentially progressing to venous, characteristically hemorrhagic infarction. Cerebral sinus thrombosis on the other hand limits the outflow of CSF, resulting in intracranial hypertension. (248) These processes also explain the typical symptoms of patients suffering from CVT. Venous infarctions become apparent in the form of epileptic seizures (approximately 40% of patients) and focal neurological deficits, including paresis, aphasia, or hemianopia, manifesting in about 50% of all patients. On the contrary, headache constitutes the most frequently observed symptom of CVT noted in 90% of patients due to the increased intracranial pressure. Decreased visual acuity is another symptom owing to this mechanism. Other clinical findings include disorientation up to loss of consciousness and altered behavior. (247, 249-251) These variable clinical manifestations of CVT necessitate imaging procedures in the diagnostical approach

to detect thrombotic changes within cortical veins and sinuses. CT- and MRI-venography facilitate the identification of occluding thrombi, while the considered gold standard, catheter angiography, should be reserved for patients with inconclusive results obtained from CT or MRI imaging. (241) Possible findings range from parenchymal brain lesions to large, space-occupying hemorrhagic infarcts of the temporal lobe. A distinguishing sign of CVT are small juxtacortical hemorrhages located right below the cortex. (252) Aside from imaging techniques, blood tests are performed, including complete blood count, chemistry panel (i.e. electrolytes, kidney and liver function parameters and glucose), PT and aPTT. (253) D-dimer values are often increased in CVT with a sensitivity of 94%, although normal values do not rule out CVT, especially in patients only complaining about headache. (254)

Treatment regimens of CVT are closely related to VTE therapy and usually imply the administration of intravenous heparins in the acute phase, followed by oral anticoagulation in the chronic phase. However, only vitamin K antagonists are indicated as oral anticoagulants and individually administered for three to twelve months, because of the yet sparse evidence regarding the treatment with DOACs. (255) In cases of large hemispheric lesions with impending herniation a decompressive neurosurgery is indicated. Endovascular treatment with chemical thrombolysis and/or mechanical thrombectomy as additional treatment options should only be implemented in cases of severe CVT or where heparin treatment is insufficient. (241, 255)

3.3.3.1.2 Arterial thrombosis and thromboembolism

Thromboembolic events within the arterial vascular system are the major causes of ischemic diseases and infarctions. Ischemia refers to a state of diminished tissue or organ perfusion due to constrictions or obstructions of the arterial blood flow. Following prolonged ischemia, the lack of oxygen results in the decay of tissue within the affected organ depending on the organ´s individual sensitivity to oxygen deficiency. These tissue necroses are called infarcts. Infarcts are generally divided into anemic and hemorrhagic infarcts. Anemic infarcts emerge from vascular obstruction in organs with end-arterial circulation and typically affect solid organs (heart, kidney, spleen). Hemorrhagic infarcts in contrast develop in organs with collaterals or dual circulation and are commonly observed in the lungs or bowels. (199) Common arterial infarctions occur as strokes, myocardial and limb infarctions.

3.3.3.1.2.1 Stroke

Strokes, also known as apoplexies, are caused by thromboemboli occluding an intracranial artery or arise due to intracerebral or subarachnoid hemorrhage. Thromboemboli cause a reduced perfusion in the brain area distal to the obstruction. In intracranial hemorrhage, the extravasating blood leads to an increase in intracranial pressure with mechanical as well as ischemic brain lesions. The consequently emerging focal neurological deficits, which typically reflect the affected region, persist for at least one hour. Cases with neurological signs of less than one hour are classified as TIA. The observed clinical symptoms must be evoked by focal cerebral ischemia or from intracranial hemorrhage to fulfill the stroke definitions. In 2015, strokes accounted for 6.2 million deaths worldwide, making it the second leading cause of mortality. While incidence rates increased over the past decades, especially in populations with limited access to health care, stroke cases declined over the past years among the affluent population. In general, stroke incidences rise with age and peak beyond the age of 65. Besides its significant mortality, stroke also represents the third leading cause of morbidity, partly because approximately 60% of survivors remain with permanent neurological impairments. Due to that fact, stroke ranks among the driving reasons for care dependency. (203, 222, 251)

Ischemic strokes are responsible for most strokes with approximately 87% of all events, whereas 13% result from intracerebral and subarachnoid hemorrhages (hemorrhagic strokes). (256) Hemorrhagic strokes often derive from hypertension and typically affect the pons, thalamus, basal ganglia, or cerebellum. Atypical brain hemorrhages in contrast impact cerebral lobes and arise from beta-amyloid deposition in vessel walls leading to degeneration. Causes of secondary bleeding encompass arterial and venous aneurysm, vascular malformation, inflammation and vasculitides as well as coagulopathies. Regarding ischemic stroke, one of the most frequent causes are cardioembolisms, constituting 20 to 25%. Clots particularly form on the walls or heart valves of the left heart, with nonrheumatic atrial fibrillation serving as the most important predisposing factor. Cerebral emboli are also triggered by carotid atherosclerosis, and the risk of stroke rises with the degree of stenosis, unless the carotid artery is almost occluded. About 10% of ischemic strokes are caused by carotid atherosclerosis. Additionally, macroangiopathies of intracranial arteries can yield both, embolic and in situ thrombotic obstruction,

blocking cerebral blood supply. So called small-vessel strokes represent about 20% of all strokes and originate from atherothrombotic or lipohyalinotic obturations of smaller cerebral arteries. Other less common initiators of stroke include dissection, sickle cell anemia, migraine, or fibromuscular dysplasia. Assured risk factors for stroke are classified into treatable and non-treatable causes. Among others, arterial hypertension, smoking, atrial fibrillation, diabetes mellitus, hypercholesterolemia or obesity are either preventable or at least treatable medical conditions providing approaches to reduce the stroke risk in affected individuals. Other factors remain invariable to medical treatment, in particular advanced age, male sex, positive family history and ethnic affiliation. Pathophysiological aspects of stroke are closely related to the blood supply of the brain. If the brain perfusion drops below the critical value of 20 mL/100 g tissue per minute, the affected brain regions become ischemic accompanied by developing neurological deficits. In this state, the impaired cellular function is still reversible, until ischemia persists for several hours or days. If the blood flow further declines <10 mL/100 g tissue per minute, the infarct threshold is reached resulting in irreversible cellular damage. The ischemic penumbra is defined as the tissue receiving just enough supply to preserve its morphology in the direct environment of the necrotizing core area without resulting in immediate cell death. Therefore, imaging of the penumbra is of great importance in the further clinical management with the potential to restore perfusion in these areas before the infarction expands. Two distinguishable pathways account for cerebral infarction. The necrotic pathway occurs in areas of very low perfusion rates with immediate cytoskeletal breakdown owing to an energy deficit. The second, apoptotic pathway proceeds in areas with diminished blood supply, such as the penumbra, with cell death occurring over the course of several days on the contrary. The symptoms of ischemic and hemorrhagic apoplexy commonly coincide, except that cerebral bleeding is more often accompanied by headache and nausea and that a neurologic deficit at onset suggests ischemia. Other typical symptoms include the loss of sensory and/or motoric function on one side of the body, with hemiparesis observed in approximately 85% of ischemic stroke patients, alongside with alterations of speech, understanding, vision or gait. Malignant cerebral infarctions are regularly associated with progressing unconsciousness and ipsi- or contralateral dilation of the pupil, because of extensive brain edema and intracranial pressure.

A rapid and targeted diagnostic approach is essential in patients with suspected stroke to evaluate the adequate therapy and preserve as much brain tissue and neurologic functions as possible. The basic management of stroke patients inside the emergency department comprises the monitoring and documentation of oxygen saturation, blood gas analysis, heart- and respiratory rates, body temperature, blood pressure and the administration of oxygen. Laboratory studies including the measurement of glucose levels, ECG and catheterization are indicated as well. A concise medical history to grade the severity of stroke via the “National Institute of Health Stroke Scale” (NIHSS) is recommended as well as knowledge regarding the time of onset and cardiovascular risk factors. Following targeted clinical examination, brain imaging is obligate to ascertain the stroke type. A native cranial CT constitutes the standard imaging procedure to rule out intracranial hemorrhage, whereas the detection of ischemic regions is often impossible early in the course of disease. If CT images are inconclusive or negative, patients should be introduced to CT-angiography and -perfusion or MRI imaging to reliably identify infarcted areas along with brain tissue showing normal diffusion but poor perfusion, indicating the ischemic penumbra. After the diagnosis of an ischemic stroke, immediate administration of rtPA for systemic fibrinolysis is indicated, if the therapy is administered within 4.5 hours after symptom onset. In selected cases, systemic thrombolysis may be implemented six hours after onset of symptoms, when preservable brain tissue is found. These therapeutic approaches can resolve the thromboembolic obstruction and thus restore perfusion in ischemic areas. In cases of large vessel obstructions or if systemic fibrinolysis fails to achieve adequate results, endovascular revascularization is an alternative therapeutic strategy. This therapy is performed in the form of intraarterial lysis or endovascular mechanical thrombectomy and may even be eligible for patients outside the prior timeframe. Additional medical support in patients suffering from ischemic stroke consists of optimization of blood pressure with target values around 160/105 mmHg, adjustment of blood sugar levels between 120-150 mg/dL and preservation of normothermia. The management of ischemic stroke patients after the acute treatment contains the prescription of a statin and an antihypertensive, with LDL cholesterol and blood pressure target values of <55 mg/dL and <130/80 mmHg, respectively. (257, 258) Above that, administration of aspirin is advised in all non-cardioembolic ischemic apoplexies within the first 48 hours after the event, whereas

cardioembolic events are treated with DOACs as a secondary prevention. As ischemic stroke represents the predominantly observed type, the precise treatment of hemorrhagic stroke is renounced in this thesis. (203, 222, 251)

3.3.3.1.2.2 Myocardial infarction (MI)

MI is a leading cause of morbidity and mortality in modern times and represents another frequently encountered entity of arterial thrombosis. MI is pathologically defined by cell death of the myocardium due to prolonged ischemia. The resulting tissue necrosis leads to the release of cardiac biomarkers, which can be detected in the serum. (259) The general types of MI are classified according to the appearance or absence of ST-segment elevations in the ECG. Patients with ST-segment elevations in adjacent leads suffer a ST-segment myocardial infarction (STEMI), compared to the forms without ST-segment elevations, namely non-ST-segment elevation-acute coronary syndrome (NSTE-ACS). The distinctive feature to differentiate between the two entities of NSTE-ACS, non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris, is the cardiac biomarker status. Positive cardiac biomarkers indicate NSTEMI, whereas biomarkers remain unchanged in unstable angina pectoris. STEMI, NSTEMI and unstable angina pectoris are summarized under the term acute coronary syndrome (ACS). (222)

Ischemic heart disease (IHD) is nowadays the leading cause of death and disability worldwide. The occurrence of cardiovascular diseases and acute MI has moved from countries with high-income to low- and middle-income countries, where over 80% of the global cardiovascular deaths take place. Despite the greater burden of risk factors in the wealthy countries, acute MI rates are lower in those countries, due to the fact of intensified preventive measures and revascularizing procedures. (222, 260-262) The main risk factors of IHD are cigarette smoking, sparse physical activity, and unhealthy diet, leading to hypertension, obesity, diabetes mellitus, dyslipoproteinemia and atherosclerosis. Advanced age and male gender are additional independent risk factors of IHD. (222)

The pathomechanisms resulting in acute myocardial infarction typically encompass the rupture or erosion of coronary atherosclerotic plaques, exposing the thrombogenic core and matrix materials of the plaque. Subsequent formation of thrombi leads to the occlusion of the affected coronary artery. The declining proportion of ruptures and increase of erosions as the main cause of MI are

assumed to derive from the availability of lipid-lowering therapies. While partial occlusions or occlusions with maintenance of blood flow through collaterals usually result in NSTEMI or unstable angina, STEMI typically follows total occlusion of the vessel. Besides, the frequency of acute MI without evidence of critical coronary artery disease is increasing and account for about 10% of cases. (260, 263, 264) Embolization of coronary arteries is a rare cause of acute MI, but can arise in patients with septal defects, infective endocarditis, myxoma or chronic atrial fibrillation. (222, 265)

Common preceding factors of acute MI include physical exercise, emotional stress or illness. The characteristic presenting symptom is severe chest pain lasting for more than 30 minutes, typically described as deep and heavy, squeezing, or crushing. The pain often radiates to the left arm, jaw, epigastrium or back, complicating the assignment of the symptoms to a certain organ. Accompanying features frequently involve sweating, nausea and emesis, dyspnea, weakness, arrhythmias, or anxiety up to fear of death. Yet, not every patient with MI presents with pain and it is often absent in diabetes mellitus or advanced age. Especially women and the elderly may present with unusual signs and symptoms, complaining acute breathlessness due to pulmonary edema, epigastric discomfort, confusion, or solely symptoms of hypotension as the cardinal sign. These symptoms can be mentioned in a relevant “teachable moment” for clinicians to spotlight the red flags to patients, who are at risk for ACS. Upon clinical examination, pale skin with sweating and cold extremities may be apparent in the mostly restless and anxious patients. Pulse and blood pressure alterations are unspecific and may range from bradycardia and/or hypotension to tachycardia and/or hypertension. Because of the partly nonspecific symptoms and the diffuse and radiating pain, aortic dissection, pulmonary embolism, pneumothorax and gastrointestinal disorders are main differential diagnoses. (222)

Patients presenting with symptoms indicative of ACS should immediately obtain a 12-lead ECG including the evaluation of ischemic changes within ten minutes after the first medical contact. Simultaneously, blood sample for the detection of cardiac biomarkers should be performed. High T-wave amplitudes, called hyperacute T-waves as well as ST-segment changes express early signs of myocardial ischemia in the ECG. The following myocardial necrosis leads to the development of new Q waves and ST-segment elevations in at least two contiguous leads, typically seen

in STEMI. Reciprocal ST depressions in the leads opposing the infarct area are an indirect sign of STEMI. Detection of a newly diagnosed left bundle branch block is considered a STEMI equivalent and should therefore be treated equally, until proven otherwise. In the case of NSTEMI, ECG changes are unspecific and may include new ST-segment depressions in approximately one third of patients. Another more common but less specific sign are T-wave changes, especially new and deep T-wave inversions (≥0.3 mV). In addition to ECG alterations, changes of cardiac biomarkers are necessary to differentiate between ACS manifestations. The repeated assessment of cardiac troponins aids in the detection of a rising and/or falling pattern of troponin levels in patients with clinically suspected ACS. For the definition of myocardial injury, at least one value of the preferred cardiac troponins I or T (cTn) must exceed the 99th percentile upper reference level. While troponin fluctuation with raised values is present in STEMI and NSTEMI, it is absent in unstable angina, allowing the distinction between the two NSTE-ACS entities. Moreover, the degree of elevation also correlates with the patient's mortality. (266)
Assessing the individual risk of a patient with ACS is recommended to evaluate the chance of an early adverse outcome. This risk classification also directs the further therapeutic approach in cases of NSTEMI. (222, 259, 260) Imaging techniques are frequently used to assess the myocardial viability, perfusion, pump function and wall movement. The recognition of structural and functional abnormalities in addition to a low-threshold access make echocardiography a key instrument in the further diagnostic approach of acute MI. Echocardiography allows the detection of frequent mechanical complications, also in hemodynamically compromised patients. Additional imaging techniques include radionuclide imaging, cardiac MRI or CT. (259)
In general, the therapeutic management of STEMI and NSTEMI is consistent, notably in respect of primary care and medication. The initial therapeutic approach for patients with suspected ACS involves bed rest, basic monitoring, and administration of oxygen in patients with hypoxemia (oxygen saturation <90%), respiratory distress or risk factors to develop hypoxemia. Sublingual nitroglycerin is administered to relief ischemic discomfort with the option of intravenous therapy in NSTE-ACS patients with persistent discomfort. In the case of STEMI, it should not be administered routinely, unless evidence of uncontrolled hypertension or congestive heart failure. (267, 268) Doses of intravenous opioids (e.g. morphine)

relief the pain and lower the sympathetic activity, improving oxygen demand, vasoconstriction and cardiac work in patients with ACS. Severe anxiety may be treated with mild tranquilizers. The early initiation of potent statins has shown beneficial results in trials and lower LDL-C levels as well as positively effecting plaque-stability. (268) Hemodynamically stable patients presenting with STEMI or NSTEMI should receive beta-blockers to lower the myocardial oxygen consumption and reduce the incidence of malignant ventricular arrhythmias in the absence of contraindications. Caution is advised in patients at risk of developing cardiogenic shock (i.e. age >70, heart rate >110 beats/min, systolic BP <120 mmHg), where death occurs more frequently. (267, 268) Additional administration of ACE inhibitors should be considered in all cases of systolic left ventricular dysfunction, heart failure, hypertension, or diabetes mellitus. Especially, STEMI patients benefit from the therapy during the first week, significantly reducing 30-day mortality. (268, 269)

Antithrombotic therapy is of utmost importance as activation of thrombocytes and the coagulation cascade play a key role in the emergence of ACS. Aspirin serves as the basis of treatment to inhibit the platelet aggregation and is administered as soon as possible in every patient without contraindications. In patients, who proceed to a primary percutaneous coronary intervention (PCI), a dual antiplatelet therapy (DAPT) is implemented, typically combining aspirin with one $P2Y_{12}$ receptor inhibitor, prasugrel or ticagrelor. These two $P2Y_{12}$ receptor inhibitors show greater potency and a faster onset of action, in addition to superior outcomes compared to clopidogrel in clinical trials. While prasugrel is considered the preferred drug in patients proceeding to PCI, ticagrelor can be administered regardless of the upcoming treatment strategy (invasive or conservative). (267, 270, 271) In the setting of invasive therapy, anticoagulation is indicated in all patients, with UFH being recommended in the routine use after diagnosis and during revascularization. Meta-analysis, which compared UFH with enoxaparin, showed a significant reduction in mortality with enoxaparin and it was further associated with a lower risk of major bleeding, especially in primary PCI. Therefore, enoxaparin is an alternative to UFH in cases with STEMI and primary PCI. (272) If no other indications require the ongoing administration of the anticoagulant, including prolonged bed rest, atrial fibrillation, or venous thromboembolism, the therapy is terminated after the procedure. (268, 273)

Regarding the reperfusion therapy, the determined durations from first medical contact to procedure deviate between STEMI and NSTEMI. For STEMI patients, primary PCI is the preferred strategy, provided the catheterization laboratory is reached within 120 minutes of diagnosis. (274, 275) If the duration to primary PCI exceeds the given timeframe, fibrinolysis using a fibrin-specific agent (tenecteplase, alteplase, or reteplase) is the therapy of choice. In this scenario, start of fibrinolysis should be within ten minutes starting from STEMI diagnosis and is most efficient within the first two hours of symptom onset. Afterwards, the patient is immediately transferred to a PCI capable center, where a routine PCI is performed preferably 2 to 24 hours thereafter. Rescue PCI is indicated in failed fibrinolysis, persistent chest pain, aggravating ischemia and hemodynamic or electrical instability. (276-278) The optimal treatment option for patients with the diagnosis of NSTEMI depends on their individual risk category. Very high-risk factors include hemodynamic instability, cardiogenic shock, recurrent chest pain, life-threatening arrhythmias, and mechanical complications of MI. These factors indicate patients to a very high-risk setting, making an immediate invasive strategy with primary PCI within two hours necessary. The early invasive approach (<24 hours) is indicated in the presence of high-risk factors, such as dynamic new contiguous ST/T-segment changes or resuscitated cardiac arrest. Only patients without any high risk characteristics are at a low risk of short-term acute ischemic events and a selective invasive strategy is preferred. (267) This patient population is submitted to stress echocardiography or stress cardiac MRI and managed according to the chronic coronary syndromes´ guideline. (279)

Following the acute phase and successful treatment of ACS, all patients without increased risk factors of bleeding or other contraindications receive DAPT for 12 months. (270, 271) Aspirin is typically recommended lifelong and lipid lowering therapies should also be maintained and adjusted where indicated. Besides the treatment with drugs, life-style modifications are of great importance in the time after diagnosis to prevent reinfarctions and contain the development of arteriosclerosis. Smoking cessation, a healthy diet, weight control, physical activity and adherence to therapy represent the major cornerstones of life-style modifications. (267, 268)

3.3.3.1.2.3 Acute limb ischemia (ALI)

Sudden cessation or marked decrease in arterial perfusion of the limb, thereby potentially threatening its survival, defines ALI. A symptom duration of two weeks

marks the cut-off to distinguish between ALI and chronic limb ischemia. (280) Global epidemiologic data are scarce but incidence ranges approximately between 14 to 20 cases per 100,000 persons per year. (203, 281, 282) Most acute arterial occlusions concern the lower extremities due to atherosclerotic plaques in afflicted arteries, which are prone to thrombosis (40%). Arterial embolism is the second leading cause, where emboli most commonly dislodge from the heart, aorta, and large arteries. Typical cardiac causes of thromboembolism to the extremities include atrial fibrillation, MI, endocarditis, or myxomas. Because of the decrease in vessel calibers at bifurcations, arterial emboli often lodge at these sites, with the femoral artery being most commonly affected, followed by the iliac artery, aorta, and popliteal and tibioperoneal arteries. Aneurysm, arterial bypass graft, traumatic arterial lesion and dissection constitute less common causes of ALI but concurrently serve as risk factors. (222, 283) Moreover, affected patients typically have a history of PAD and feature its risk factors, such as hypertension, hypercholesterolemia, diabetes, renal insufficiency, and smoking. (280) The etiology of ALI also tremendously impacts its severity, as patients with local thrombosis and preexisting PAD have frequently developed an adequate collateral circulation. In contrast, arterial emboli often occlude the entire lumen, resulting in severe symptoms and the need of immediate revascularization. Depending on the severity of the occlusion, specific signs and symptoms are indicative of ALI upon clinical examination of the extremity. These are summarized under the mnemonic the “six Ps”, and include pain, pallor, pulselessness, paresthesia, paralysis, and prostration or perishing coldness. Especially the loss of sensory and motor function are symptoms of a threatened limb. Rutherford classification serves as a widely applied grading tool for a quick assessment of the severity degree and further clinical management of ALI. (280) The classification combines clinical examination findings (i.e. sensory loss and motor deficit) with Doppler flow signals arteries to differentiate between a viable, not immediately threatened (grade I), marginally threatened (grade IIA), immediately threatened (grade IIB) and irreversibly damaged (grade III) limb. (282) As time is crucial in the rescue of the affected extremity, the appropriate further imaging modality must not delay treatment. Although duplex ultrasonography can accurately detect leg’s artery occlusions proximal to the knee, it is currently not recommended to exclude ALI solely based on ultrasonography. Therefore, CTA or MR angiography (MRA) is the imaging procedure of choice to confirm ALI and visualize the extent of

arterial occlusion following clinical examination. Hereby, CTA and MRA also allow the evaluation of potential causes of ALI and to plan subsequent treatment procedures. In general, patients with suspected ALI should be treated in vascular centers, which provide 24-hour open and endovascular interventions. Initial management comprises the initiation of sufficient analgesia and intravenous UFH combined with intravenous rehydration and supplementary oxygen. The further revascularization approach depends on the Rutherford grade. While patients with ALI grade I and IIA need a timely treatment, cases with grade IIB are referred to urgent revascularization. Revascularization techniques range from surgical thrombo-embolectomy, surgical bypass, percutaneous catheter directed thrombolysis, and thrombus aspiration or mechanical thrombectomy. The technique of choice depends on factors regarding the vascular team, as well as the patient, including ALI duration and severity, comorbidities, and therapy related risks. (280) In patients with grade III ischemia, where irreversible limb infarction with tissue necrosis and permanent nerve damage has frequently occurred, primary amputation is often inevitable. (282) In contrast, if revascularization was successful within six hours of symptom onset, preservation of the limb is ensured in 96% of cases. (203) A therapy-associated complication worth mentioning is reperfusion injury, characterized by limb edema and introduction of harmful metabolites into the systemic circulation after prolonged ischemia. The sequelae range from increasing limb compartmental pressures leading to the development of compartment syndrome to arrhythmias and crush syndrome. (284)

4 Methods

A literature search of PubMed (MEDLINE), the Cochrane Library Database, Google scholar, and ClinicalTrials.gov was performed between February 2021 and September 2022. Search queries included free text as well as “Medical Subject Headings” (MeSH), where applicable to receive both, already indexed articles and not yet categorized publications. The following keywords were utilized without limitation: “Covid-19”, “Covid”, “SARS-CoV-2”, “vasculopathy”, “vasculitis”, “coagulopathy”, ”thromboembolism”, “endothelial activation/dysfunction” or “immunothrombosis” and “thromboinflammation” in different combinations using Boolean operators. Entity specific searches included terms such as “stroke”, “myocardial infarction”, “acute limb ischemia”, “thromboembolism” and “vasculitis”

associated with Covid-19. Search filters were applied to exclude languages other than English and German and in the case of Covid-19 or SARS-CoV-2 associated search queries, the received results were filtered for publications since 2020. Included article types range from laboratory studies and case series, over observational studies, and cohort studies to controlled clinical trials and meta-analysis.

5 Results

Vasculopathies are frequently reported complications during the disease progression in patients with Covid-19, which may worsen outcomes and increase mortality. VTE are the most frequently reported vasculopathies within Covid-19 patients while most arterial thromboembolic events did not differ between patients with and without Covid-19. (285, 286). The potential impact of infections on atherogenesis constitutes another finding, which reflects the far-reaching effects on the cardiovascular system. (287) In addition, the infection-initiated inflammatory processes may also trigger infection-associated vasculitides, while genuine vasculitides related to SARS-CoV-2 are rare findings and occur predominantly as cutaneous small vessel vasculitis and Kawasaki-like disease, typically associated with MIS. (205, 288, 289) The upcoming paragraphs give an overview on recent pathophysiological pathways and clinical data of Covid-19 associated vasculopathies.

5.1 Pathophysiology of Covid-19 associated vasculopathy

During the pandemic, tremendous advances were accomplished regarding the pathophysiologic mechanisms of Covid-19 associated ARDS and vasculopathies. To date, it is assumed that several complex processes, triggered by the virus itself and immune-mediated interactions, are involved resulting in vascular complications. The most significant endogenous systems involved in the development of vasculopathies are the endothelium, the immune system, with particular emphasis on neutrophils, as well as the coagulation system. The overwhelming release of pro-inflammatory mediators with a subsequent procoagulant state is also called immunothrombosis. Thereby, thromboembolic events and vasculitides are triggered and occur throughout the vascular system.

5.1.1 Endothelial dysfunction

Endothelial cells have immense impact on the pathogenesis of severe Covid-19 as they express the SARS-CoV-2 binding receptor ACE-2 and contribute to inflammation (see subchapter 3.2.2). Early investigations of Varga et al. (290) demonstrated this endothelial involvement in a case series by detecting viral inclusion structures in combination with an accumulation of inflammatory cells across vascular beds of different organs. Thus, they discovered endotheliitis as a potential key pathophysiologic mechanism in severe courses of Covid-19. Staining patterns of histological analyses also showed apoptosis of endothelial and mononuclear cells to a considerable extent. They concluded that direct viral infection of endothelium or immune-mediated processes drives immune cell recruitment. This results in pervasive endothelial dysfunction and apoptosis ensuing microvascular imbalance with organ damage, inflammation and a procoagulant state. (290, 291) However, doubts arise regarding the validity of the detected intracellular viral structures using electron microscopy (EM). (292-294) The authors point out the strength of EM to identify intracellular pathogens including SARS-CoV-2 on condition of pertinent expertise when interpreting these images. Apart from this, it is not contradictory to the opinion that endothelial cells contain viral particles during severe Covid-19, as Dittmayer et al. (292) visualize in their comment.

Conversely to Varga et al. (290), autopsies of ten patients could not detect spike protein mRNA of SARS-CoV-2 in pulmonary endothelial cells. In vitro studies support the assumption that endothelial cells are not commonly infected in Covid-19. (295, 296) Experiments with human umbilical vein and lung endothelial cells demonstrated significantly lower expression levels of ACE-2 and TMPRSS2 compared to immortalized epithelial cells. (296) In more physiological in vitro models similar to pulmonic epithelial-endothelial barrier, co-cultures were established and infected. Viral replication with production of infectious virions was only confirmed in the epithelial monolayer, but an increase in pro-inflammatory cytokine secretion (IL-6, TNF-α, the C-X-C motif chemokine ligand 10) and the intercellular adhesion molecule 1 expression was measured in the endothelial cell layer. (296, 297) The apoptotic cell death, ascertained in the aforementioned case series, was also corroborated by the observation that endothelial cells are infected but only upon high viral titers triggering apoptosis. (296) A meta-analysis on the histopathologic findings revealed 33 cases of vascular injury within the lungs of 157 Covid-19

patients, 28 thereof described as endotheliitis which further supports the hypothesis. (298) No study evaluated yet the viral burden, which impacts endothelial infection, within the respiratory tract or other sites of endothelial involvement in patients. Analyses of lung autopsy samples via RNA in situ hybridization estimated a viral copy number of more than 500,000 viral genomes/mm^2 across many lung tissue areas. (299) Of note, these areas of high viral load lacked pneumocytes, probably due to preceding infection and decay as part of the natural progress of severe Covid-19.

5.1.2 Immunothrombosis

Following the primary phase of microvascular disturbance in severe courses, endothelial activation and innate immune system recruitment stimulate the initiation of the coagulation cascade. This progression is considered as a key pathologic mechanism towards the procoagulant state with formation of microthrombi hypothesized in aggravating Covid-19. (300, 301) The concept of a specific interaction between inflammation and coagulation is not unique to Covid-19 but has already been described in the literature, especially in regard to ARDS and sepsis. On a molecular basis, a subfamily of G protein-coupled receptors, called protease-activated receptors (PARs), connect the inflammatory processes with pro-coagulative mechanisms. PARs are expressed on the cell surface of immune cells, platelets, and endothelial cells, which orchestrate the thrombo-inflammatory processes. (302, 303) Their activation via thrombin and additional coagulation-related molecules triggers the activation of platelets and expression of numerous pro-inflammatory genes and adhesion molecules. (304, 305) Thereby, both systems initiate a coordinated response to tissue damage and cellular injury due to trauma or pathogens. However, studies indicate that a dysregulation of immunothrombosis might be the cause of devastating complications, including stroke, DVT, and DIC during sepsis. (306)

In literature, two terms are frequently used to describe this cooperation of inflammation and coagulation within microvessels: immunothrombosis and thromboinflammation. Of note, while several authors describe the pathomechanism as immunothrombosis, others designate the identical process as thromboinflammation. The following paragraph aims to clarify the coexisting terms. Tanguay et al. (307) introduced the phrase “thrombo-inflammatory reactions” to

describe the interaction between platelets and leukocytes triggering in-stent restenosis. (307, 308) According to a more recent review, the sole concomitance of thrombosis and inflammation generally known in different disorders (e.g. thrombophlebitis or sepsis) defines thromboinflammation, thereby extending the term´s relevance. (309, 310) In contrast, Engelmann and Massberg (306) define immunothrombosis as a specific response of the innate immune system in cooperation with the coagulation system to destroy pathogens and restrict dissemination especially within microvessels. (306, 309) Considering both established definitions, thromboinflammation might serve as the general term to outline interactions between inflammation and thrombosis in various intravascular disorders. Instead, immunothrombosis rather designates a precisely coordinated process of these systems to prevent further pathogenic destruction and organ damage. In the following, immunothrombosis is therefore used as the primary term to describe the hypothesized microvascular disturbance in Covid-19 pathogenesis.
Many authors emphasize immunothrombosis as the key process in the formation of microthrombi across vascular beds endorsing its relevance in severe Covid-19. (309, 311, 312) It is already known that pro-inflammatory cytokines (IL-1β, IL-6, IL-18 and TNF-α), extensively released during immune response (see chapter 3.2.2) trigger endothelial activation and dysfunction in sepsis and viral infections. (309, 311, 313, 314) According to Cenko et al. (311), activated endothelial cells express tissue factor (TF) and release von Willebrand factor (vWF) and P-selectin (also known as [soluble] CD62P) containing Weibel Palade bodies. Upregulation of P- and E-selectins on the endothelial cell surface recruit and activate neutrophils and monocytes, which in turn express and release additional activated TF at the virally affected microvessels. (311) Bonaventura et al. (309) reported the ability of monocytes to identify pathogens via pattern recognition receptors and present activated TF. The following high density of TF initiates the TF pathway (or extrinsic pathway) of the coagulation cascade. In a mechanism called NETosis, recruited neutrophils unleash neutrophil extracellular traps (NETs), which trap SARS-CoV-2 and activate factor XII (FXII) to promote the contact or intrinsic pathway. Moreover, neutrophil elastase and MPO, components of NETs, cleave and inactivate endogenic anticoagulants (tissue factor pathway inhibitor, antithrombin III and thrombomodulin) and NET-bound vWF promotes platelet recruitment, thereby enhancing coagulation. In addition, also the complement system is involved in

immunothrombosis, as the complement components C3a and C5a can activate platelets. (306, 311)

Cenko et al. (311) further assume a participation of the renin-angiotensin system (RAS) in promoting the pro-inflammatory and procoagulant state. Their presumption, however, is based upon animal models and already existing explanatory models of ACE-2 internalization and down-regulation during SARS-CoV and viral infections in general. (315, 316) As a consequence, angiotensin II (Ang II) levels rise, whereas less is converted to angiotensin (1-7) (Ang 1-7). This could lead to imbalances between the two main RAS axes with overactivated Ang II/ Ang II type 1 receptor and under activated Ang 1-7/ MAS receptor (MASR) axis. (311) Thus, a pro-inflammatory and vasoconstrictive state is created, since it lacks its counterbalance (Ang 1-7/MASR), which promotes anti-inflammatory and vasodilative effects. (317) However, a recent meta-analysis by Pucci et al. (317) demonstrated an overactivated Ang 1-7/MASR axis in Covid-19 patients with elevated Ang 1-7 concentrations compared to controls. In severe courses, the levels were already higher at the time of hospital admission than in mild cases and increased further during the following ten days of hospitalization. At the same time, Ang II levels were also modestly raised.

The central role of immunothrombosis is also confirmed by autopsy analyses, which explored the cellular and molecular composition of microthrombi. Confocal microscopy discovered abundant intravascular neutrophils associated with platelets and fibrin within the microvessels. Of note, these were not limited to the lungs but also found in renal and cardiac vessels. (318)

5.1.3 Biomarkers

In regard to the immunothrombotic mechanisms and concomitant mortality of severe Covid-19, several studies investigated potential biomarkers which not only reflect the involved systems but are also of prognostic value. These include parameters of coagulation, fibrinolysis, endothelial activation as well as markers of platelet and complement activity.

In a cross-sectional study, Goshua et al. (319) compared laboratory markers indicative of endotheliopathy and coagulopathy between SARS-CoV-2 positive ICU patients, positive non-ICU patients and asymptomatic controls. Their data revealed significantly elevated markers of coagulopathy and endotheliopathy in the form of

D-dimer, thrombin-antithrombin complex (TAT) levels and vWF activity, respectively, in hospitalized patients. Of those, patients admitted to the ICU had the greatest increases. Additional studies yielded likewise D-dimer results, with markedly elevated levels in severe Covid-19 cases. (318, 320, 321) Moreover, D-dimer levels not only served as the best marker to distinguish Covid-19 status among ICU patients (positive vs. negative) but concentrations also correlated significantly with disease severity. (318, 320) Measurements of plasma biomarkers showed a considerable rise in soluble P-selectin, as a marker of endothelial cells and platelets, and soluble CD40-ligand (sCD40L), as a marker of platelet activation, in ICU patients related to asymptomatic controls. (319) The role of platelet activation during severe disease is further emphasized by analyses revealing significant alterations during the course of disease in patients admitted to the ICU. While sCD40L plasma levels decreased over time, soluble P-selectin increased significantly during a 2-week ICU stay in survivors. (322) However, besides the small Covid-19 cohort of 29 patients, the comparison group composed of convalescent patients (eligible 14 days after symptom resolution) limits the validity of that study. The fact that P-selectin levels did not differ from ICU patients on day one and recovered individuals adds doubts about the significance of P-selectin as an acute platelet activation marker. (322) Moreover, sustained endothelial dysfunction reflected by circulating endothelial cells and elevated endothelial biomarkers is also evident in convalescent Covid-19 patients. (323, 324) These data indicate considerate usage of a convalescent control dependent on the analyzed biomarkers. Another study supports this hypothesis which revealed altered parameters of endothelial dysfunction and changes in vascular homeostasis six months after confirmed SARS-CoV-2 infection and inpatient treatment. (325) Additionally, these post-Covid-19 patients had higher levels of vWF antigen and activity, homocysteine, as well as certain endothelial microparticles and suffered from increased arterial stiffness compared to a healthy control group. Post-Covid-19 patients further featured a higher number of elevated inflammatory parameters, including CRP, ESR and IL-6. Interestingly, the paper also analyzed differences between post-Covid-19 patients and those with atherosclerotic cardiovascular diseases, detecting significantly more frequent microvascular changes (capillary ramifications, loss, caliber variability, and elongation) in the former. They concluded

that the different SARS-CoV-2 pathomechanisms affect the microvasculature persistently and thereby change vascular reactivity.

Additional biomarkers of endothelial dysfunction, soluble thrombomodulin (sTM), as well as P-selectin markedly correlate with vWF antigen (vWF:Ag), which is in accordance with their origin from endothelium. In respect of the biomarkers´ prognostic value, Goshua et al. (319) investigated that both sTM and vWF:Ag significantly correlated with mortality across all severity cohorts. Their results are emphasized by a meta-analysis showing a rise in vWF:Ag levels in proportion to illness severity. Pooled data revealed the lowest concentrations in healthy controls in contrast to levels in non-survivors, who also exceeded ICU/severely ill patients. (326) Data of ADAMTS13, the cleaving protease of vWF multimers, coincided with the vWF results. While severe and fatal Covid-19 cases featured substantially lower ADAMTS13-activities (ADAMTS13:Ac) than moderate cases, vWF:Ag concentrations increased. (327, 328) In consequence, the calculated ratio of vWF:Ag/ADAMTS13:Ac augmented alongside illness severity throughout all cohorts. Both parameters, ADAMTS13:Ac and vWF:Ag/ADAMTS13:Ac ratio, indicate severity differentiation (severe vs. moderate) as well as prediction of in-hospital mortality. (328) However, ADAMTS13:Ac and vWF:Ag expressed as percent were again calculated in relation to plasma levels of convalescent controls. Data regarding the analyses of vWF multimers support the hypothesis of thrombotic thrombocytopenic purpura (TTP)-like courses in Covid-19. One study shows that large and ultralarge vWF multimers are markedly reduced in Covid-19 patients compared to healthy controls. This resembles their accumulation within microthrombi as seen in TTP. (327)

Additional reports provided evidence of “complement over-activation and consumption” by showing increasing levels of complement factor C3a while C3 declined in fatal Covid-19 cases compared to ICU-survivors. (328, 329) Moreover, patients with high C3a/C3 ratios in combination with low ADAMTS13 exhibit a significantly lower chance of survival. (328)

Further investigations detected the abovementioned sTM as a suitable parameter to predict patient outcome. As sTM significantly correlated with mortality when solely analyzed within the ICU cohort, the cohort´s median value of 3.26 ng/mL served as a threshold to divide patients in two groups. Patients with high sTM (>3.26 ng/mL) exhibited a significantly higher in-hospital mortality when compared to the low sTM

cohort. (319) This is consistent with a longitudinal biomarker analysis which identified higher plasminogen activator inhibitor 1 (PAI-1) levels, longer clot lysis time, and reduced plasminogen concentrations in addition to sTM to predict mortality. Especially, clot lysis time increased during the ICU stay in the cohort of patients who died, whereas it declined in survivors. (320) However, only 14 Covid-19 patients were included in the study and further division was conducted for mortality analyses. Nonetheless, a meta-analysis including the data of Goshua et al. (319) confirmed the significant correlations between levels of vWF antigen, sTM, and PAI-1 and poor outcomes, suggesting the addition of high tissue-type plasminogen activator concentrations as another important surrogate of endothelial dysfunction. Notably, poor outcomes were not restricted to mortality in this analysis but included ICU admission, severe illness, deteriorating respiratory status or need of mechanical ventilation. (326)

5.1.4 Neutrophil extracellular traps (NETs)

The abovementioned contribution of neutrophils and NETs towards immunothrombosis in Covid-19 is not fully understood and central content of ongoing research. Neutrophils, which are activated by pathogens, a pro-inflammatory milieu, antibodies, or other activated cells release NETs in a reaction called NETosis. NETs consist of decondensed chromatin with histones and microbicidal elements such as neutrophil elastase and MPO, building a structure to bind pathogens as well as endogenous cells and mediators. Comparable to immunothrombosis, NETs contribute to pathogen containment under regulated conditions, while exaggerated release is associated with coagulopathy and aggravating complications. Therefore, several studies investigated neutrophil activation and NETs release in Covid-19 patients compared to healthy controls.

Studies demonstrated significant neutrophilia in severely affected individuals and a rise in activated neutrophils with a low-density phenotype and formation of multicellular aggregates in all hospitalized Covid-19 patients. This specific subtype, also called low-density granulocytes, is prone to spontaneously form NETs. (330-333) Upon NETosis, different surrogates become detectable in the patients´ plasma. The frequently measured NET markers include cell-free DNA (cfDNA), DNA-myeloperoxidase (DNA-MPO) complexes, DNA-neutrophil elastase, and citrullinated histone H3 (citH3), with the latter three being specific for NETs. (332,

334) Significantly elevated levels of all markers in plasma of hospitalized patients (i.e. moderate to severe illness) were demonstrated throughout different trials in comparison to healthy individuals. (332-338) Especially the measurement of DNA-MPO complexes is primarily used to reflect soluble NET concentrations. In vitro analyses confirmed that neutrophils of Covid-19 patients extrude higher NET concentrations than those of healthy controls, despite normalization of cell numbers. The results were further visualized by confocal microscopy analyses. (333) By this means, neutrophilia paired with elevated NETs release intensifies potential complications of extensive NETosis and immunothrombosis in severe Covid-19 cases. Additionally, in the study of Leppkes et al. (332), neutrophil elastase activity enabled the differentiation between healthy individuals and the hospitalized Covid-19 cohort. DNA-MPO complex levels were also significantly higher in non-survivors compared with Covid-19 survivors and further correlated directly with the SOFA score. (336) Moreover, rising NET-markers correlated with increasing need for respiratory support, and patients requiring mechanical ventilation experienced significantly higher levels of cfDNA and DNA-MPO than patients on ambient air. (334, 337) In contrast, citH3 concentration and absolute neutrophil count did not significantly differ between these cohorts. (334) Ng et al. (337) underlined the potential of NET-biomarkers as prognostic indicators by demonstrating that marked elevation at admission was associated with poor outcomes (admission to ICU and/or short-term mortality).

Autopsy samples of lung tissue emphasized the contribution of neutrophils and NETosis in immunothrombosis, revealing pulmonary vessel occlusions by cell-rich clots with associations of citH3-positive neutrophils and platelets. The specimens further demonstrated aggregated NETs and partially denuded vessel walls, indicative of endothelial damage adjacent to NET extrusion. Of note, these NET-aggregates were also found in damaged glomeruli and hepatic periportal fields. (332) Data from proteomic analyses of postmortem lung tissue revealed enhancement of pathways which contribute to neutrophil, platelet, and complement activation in combination with elevated FXII levels. In contrast to non-Covid-ARDS cases, immunostaining visualized robust colocalization of activated FXII and citH3 in pulmonary vessels of deceased Covid-19 patients, highlighting both the proteome analyses as well as FXII activation within NET structures during immunothrombosis. (335) These interactions of neutrophils, platelets, and clotting factors further

strengthen the complex interplay between the innate immune system and coagulation to trigger microthrombosis. Additional data showed a significantly lower DNase activity, crucial to degrade NETs, in Covid-19 plasma samples than in healthy controls. In fact, compared to donor plasma and recombinant human DNase I, Covid-19 plasma was incapable of degrading NETs in vitro. The defective NET clearance promotes NET accumulation and causes sustained FXII activation. (335) Results of in vitro experiments revealed a strong induction of NETosis in neutrophils from healthy individuals when exposed and cultivated with Covid-19 patient plasma or sera. By contrast, exposure to heterologous control sera did not provoke NETosis. (334, 336) This might reflect the capability of high cytokine and chemokine concentrations within the patients´ sera to induce NETosis. However, data of Skendros et al. (338) contradict these results by emphasizing a platelet-rich plasma dependent NET formation in control neutrophils. Only in the case of stimulation with platelet-rich plasma from Covid-19 patients, neutrophils were expressing NETs, while serum or plasma without platelets failed to trigger efficient NET formation. However, plasma samples of only four Covid-19 patients were included in their experiment in contrast to more than 20 in the abovementioned studies. Another interesting finding was the observation that neutrophils only released NETs when cultured with viable but not inactivated SARS-CoV-2, in addition to demonstrating signs of direct neutrophil invasion. (333)

Investigations regarding correlations between NET-markers and surrogates of inflammatory and procoagulatory processes yielded deviating results. Some trials noted robust correlations of DNA-MPO with total leukocytes and neutrophil count, CRP, and LDH, as well as D-dimer as a marker of a procoagulant state. (335, 337) Conversely, patient samples in the study of Zuo et al. (334) showed no significant associations of DNA-MPO with CRP, LDH or D-dimer. Moreover, other studies revealed positive correlations of DNA-MPO complexes to TAT, TNF-α and IL-6. (337, 338)

Two trials also measured NET biomarkers in convalescent patients four to six weeks and four months after infection, respectively. One study demonstrated comparable DNA-MPO levels in healthy controls and convalescent patients four to six weeks after a positive SARS-CoV-2 PCR result. (336) The second study revealed normal concentrations of NET markers four months after infection. (337) Their findings might have significant implications in synopsis with the data of Fogarty et al. (324)

which detected a sustained endotheliopathy approximately ten weeks after infection. This trial also revealed similar NETosis markers between convalescent patients and controls, however, measurements were restricted to DNase activity and extracellular DNA, which are not specific to NETosis.

Several studies further examined the potential of different agents to contain overshooting NETosis and NETs formation in vitro. Covid-19 plasma induced NET formation was significantly decreased by the NET-inhibitory peptide neonatal NET-inhibitory factor. (336) Addition of DNase I degrades NETs in vitro and is accompanied by a 50% reduction of FXIIa formation. (335) Leppkes et al. (332) discovered that addition of UFH expedited NET clearance by DNase I in vitro, and previous experiments also attributed LMWH the ability to annul NET formation by neutrophils. (339)

5.2 Covid-19 associated vasculopathies

Since the beginning of the pandemic, thromboembolic events have been frequently described among hospitalized patients with Covid-19. Although VTE is more common, arterial thromboembolisms (ATE) are also reported to a considerable extent in hospitalized Covid-19 patients. As mentioned above, endotheliitis is a common feature of Covid-19 and contributes to the development of thromboembolic events. Thereby, it also constitutes the most significant type of inflammatory vasculopathy. However, further vasculitides, including Kawasaki-like disease and cutaneous manifestations have also been reported. Since vasculopathies complicate the course of disease in other acute medical illnesses, significant effort was expended to ascertain the clinical characteristics of Covid-19 associated thromboembolism. In addition to the described physiopathology of the apparent hypercoagulable state, further research focused on clinical considerations of vasculopathies. With progression of the pandemic, emphasis was put on the investigation of risk factors associated with thrombotic events and their prognosis, especially in hospitalized individuals. Therefore, several studies obtained information to identify risk factors and determine their incidence and repercussions on patient management and prognosis. The acquired knowledge contributes to an optimized patient care and shapes the therapeutic approach in hospitalized Covid-19 patients with and without thrombotic events or vasculitides.

5.2.1 Epidemiology

Frequency of Covid-19 related VTE ranged between 13% to 14.7% across two meta-analyses of observational studies with a reported pooled prevalence of PE of approximately 8% and of DVT of approximately 11%, respectively. (340, 341) Subgroup analysis revealed significantly higher VTE rates in ICU patients compared to a mixed cohort or non-ICU patients in both meta-analyses (23.2% vs. 9% and 31% vs. 7%, respectively). In one of the largest retrospective observational studies, VTE rates of more than 370,000 hospitalized Covid-19 patients were investigated. (342) While the overall incidence of VTE was 4.6%, detection rates in the non-ICU compared to the ICU cohort were 4% and 10.7%, respectively. Additionally, screening approaches significantly alter detection rates in hospitalized patients. The prevalence of VTE was markedly higher in studies with a systematic screening approach of all patients than in those which tested merely upon clinical suspicion. Zhang et al. (341) demonstrated significantly improved detection rates in screened ICU patients with a PE and DVT prevalence of 37% and 40%, respectively, as opposed to 12% and 11% by testing on clinical suspicion. Despite significantly higher frequencies of DVTs upon screening of non-ICU cohorts, differences in PE screening versus testing on suspicion remained nonsignificant. Regardless of the two test strategies, ICU patients developed VTEs significantly more often compared to non-ICU patients. The finding of higher detection rates upon screening is strengthened by another meta-analysis, which screened all Covid-19 patients for VTE with compression ultrasonography and CTPA to detect DVT and PE, respectively. (343) The reported prevalence of PE and DVT reached 32% and 27% within a mixed cohort of hospitalized patients. Besides revealing substantially increased VTE cases due to the screening approach, the meta-analysis by Kollias et al. (343) demonstrated higher PE than DVT rates. As DVT usually constitutes the major cause of PE, this finding could indicate an additional formation of in-situ pulmonary thrombi in the setting of Covid-19. (344) Indeed, data from a pre-Covid-19 era reported a prevalence of 60.1% for DVT in patients with acute PE. (345) Conversely, data of a recent meta-analysis revealed only a DVT prevalence of 11% in Covid-19 patients with PE, supporting the assumption of additional in-situ thrombus formation within pulmonary vessels. (346) Contradicting the conclusion of a significantly elevated risk of VTE in Covid-19, a meta-analysis compared incidences in Covid-19 versus non-Covid-19 cohorts. The estimated cumulative

relative risk (RR) for VTE of 1.18 (95%CI 0.79–1.77; p = 0.42; I^2 = 54%) revealed no significant difference between the two cohorts. (285) Subgroup analyses of PE and DVT risk also remained nonsignificant. However, ICU patients with Covid-19 had a significantly higher risk of developing VTE compared to those without (RR 3.10; 95%CI 1.54–6.23), and the same applied to the overall cohort comparison when solely prospective studies were included (RR 2.74; 95%CI 1.18–6.40). In comparison, another meta-analysis of twelve studies, partly including the abovementioned studies, demonstrated a significantly higher risk difference (RD) for VTE when hospitalized Covid-19 patients were compared to non-Covid-19 patients (0.06, 95% CI 0.01–0.11, p = 0.011, I2 = 97%). (286) Data of the ICU cohorts yielded similar results, with a 16% increased risk in patients with Covid-19 compared to those without and 11% more risk of developing PE.

ATE range from stroke, myocardial infarction, and thromboses of the aorta, to acute limb and mesenteric ischemia. Except for stroke, which shows higher rates in SARS-CoV-2 infected individuals, incidences of arterial thromboses (MI, ALI, other ATE) do not differ between hospitalized Covid-19 patients and non-Covid-19 cases with or without non-Covid viral pneumonia. (347, 348) One meta-analysis revealed overall ATE rates of approximately 4%. (340) ATEs included myocardial infarction/ACS (1.1%), ischemic stroke (1.6%), and other ATE, combining visceral or limb ischemia (0.9%). However, no data of subgroup analysis to compare ICU with non-ICU cohorts were available. A large retrospective cohort study supports the data of ischemic stroke and other ATEs with prevalences of 1.6% and ≤1%, respectively. (349) In contrast, their overall incidence of ATE exceeded 11% in all hospitalized Covid-19 patients, owing to a high rate of detected MI with 8.9%. Of interest, the consecutive patients in this study suffered from more ATE than VTE (6.2%). Similarly, a systematic review by Jenner et al. (350), which combined data from the ICU with over 2900 patients, revealed an incidence of 12% for ATE, with 8% due to MI. Ischemic cerebrovascular events occurred in 3% and limb or mesenteric infarction accounted for 2.5% of cases.

Studies on the epidemiology of Covid-19 associated vasculitides are scarce, as vasculitides other than endotheliitis are rare manifestations in Covid-19. The most encountered include cutaneous small vessel vasculitis, often in the form of „Covid toes”, and vasculitis in a Kawasaki-like disease. (288, 289) The latter being typically associated with MIS, which constitutes the most prevalent vasculitis syndrome

related to SARS-CoV-2 with approximately 316 cases per 1,000,000 infections in individuals younger than 21 years. (351) These results are supported by data of Karagiannidis et al. (352) who calculated incidences of 0.07% in Germany for persons under the age of 18.

5.2.2 Risk factors

As the knowledge of specific risk factors for thromboembolic events is crucial for prevention and treatment, especially in hospitalized patients with Covid-19, several studies addressed their patients' risk profiles. While elevated levels of D-dimer at admission, male gender, and cancer were detected as risk factors throughout several studies, evaluation of other factors yielded discordant results. Particularly, D-dimer levels beyond 500 ng/mL were significantly associated with any thrombotic event. (342, 346, 349, 353) Interestingly, some studies reported a slightly increasing risk with advancing age (odds ratio 1.04) with those aged 60 to 69 years experiencing the highest odds. (342, 353) On the contrary, this weak association of advanced age and the risk for PE became nonsignificant in another meta-analysis if a lower-quality study was omitted. (346) Moreover, Bilaloglu et al. (349) detected Hispanic ethnicity and coronary artery disease as risk factors associated with both VTE and ATE, in addition to age, gender, and higher D-dimer values. Otherwise, typical comorbidities which increase the risk for VTE, such as BMI, hypertension, and diabetes, showed no significant association in Covid-19. Only obesity was identified as a risk factor in one study. (342) Other specified risk factors for VTE were Black ethnicity, a longer interval between onset of disease and admission, a ≥1.5-fold increment of D-dimer, and HIV. (342, 353) Thrombotic events in turn also impact the further course of disease. Diagnosis of PE significantly increased the risk of ICU admission and mechanical ventilation compared to Covid-19 patients without PE, whereas the risk of mortality remained nonsignificant. (346) The majority of included papers, however, found significant associations between death and VTE in general, with greater odds of in-hospital mortality (OR 1.35) as well as a pooled odds ratio for death of 2.1 in relation to non-VTE cases. (342, 343) Similarly, mortality in the case of any thrombotic event (arterial and venous) was significantly higher than without (43.2% vs. 21%), and adjusted hazard ratios underlined thrombosis as an independent risk factor (1.82; 95% CI, 1.54-2.15; P < .001). (349) Of note, the hazard ratio for ATE exceeded VTE.

5.2.3 Covid-19 associated venous thromboembolism

As most clinical guidelines combine their recommendations on DVT and PE management in Covid-19 patients, both are presented hereafter under the term VTE. As already mentioned above, the incidence of VTE in Covid-19 patients is especially high in the most severe cases admitted to the ICU. Studies attribute Covid-19 patients 3-6 times higher VTE rates when compared to a non-Covid-19 ICU cohort. While the incidence of VTE exceeds 20%, non-Covid-19 cases exhibit rates between 5-10%. (340, 341, 354-356) Moreover, PE rates are elevated as opposed to H1N1 influenza, SARS or MERS infections. (357)

Despite their high frequency, few data on the signs and symptoms of VTE in Covid-19 are available. Data of the RIETE registry, a prospective registry of consecutive patients with symptomatic and confirmed acute VTE which also incorporates Covid-19 patients, listed the typical features of PE. (358) Among the 379 SARS-CoV-2 positive patients with PE, 20% suffered from hypotension with systolic blood pressure <100 mmHg or requirement of vasopressors, and 18% were tachycardic (heart rate >110/min). Echocardiography revealed pulmonary artery pressure >40 mmHg in 36% of patients, and 33% had right ventricular dysfunction. However, the similar symptoms of Covid-19 pneumonia and PE with dyspnea, tachypnea, tachycardia, cough, or chest pain can obscure and complicate the clinical diagnosis of PE. In this study, the median time interval between hospitalization and VTE diagnosis was ten days. Of note, 88% of patients were receiving thromboprophylaxis at the time of VTE diagnosis, which again underlines the excessive thrombogenicity of moderate to severe Covid-19. Regarding the signs and symptoms of DVT, one study noted lower limb pain or edema in 58% of patients, which constituted the second most common complaint after dyspnea. (359) In general, DVT symptoms in Covid-19 are similar the conventional type. (360) Data on the typical locations of VTE showed that most patients in a non-Covid-19 cohort suffered from central PE, while segmental and subsegmental forms were the dominating locations in Covid-19 patients. (355, 361-363) In the case of lower extremity DVT, one study reported distal DVT as the most frequently DVT subtype observed in Covid-19, with 65% thereof within the intramuscular veins. (364) In comparison, in the study of Jiménez et al. (359) distal and proximal DVT were comparable and 22% of cases featured both, proximal and distal DVT. Instead, proximal DVT is the leading form in non-Covid-19 cases. (365) Throughout different studies, elevated D-dimer levels were

the most significant deviating laboratory parameter in Covid-19 patients with detected VTE compared to cohorts without. (359, 366, 367) Despite the already pathologically elevated D-dimer levels in hospitalized Covid-19 cohorts, including the control groups of the following studies (SARS-CoV-2 positive, VTE negative), VTE patients displayed levels extending beyond those. According to one study, 72.3% of DVT cases presented with D-dimer concentrations beyond 3000 ng/mL, and levels >5000 ng/mL were robustly related to DVT (OR 19.44). (359) Whyte et al. (367) detected higher D-dimer concentrations in PE patients, with a median value of 8000 ng/mL. Furthermore, CRP concentrations were also significantly elevated in both DVT and PE, while prothrombin time was comparable to patients without VTE. (359, 367) However, guidelines on the approach to VTE in Covid-19 recommend against D-dimer and biomarker-based management in general, which is endorsed by at least two published recommendations. (368, 369) The diagnostic approach is rather built on clinical features, which are indicative of DVT or PE, such as abrupt and unexplained clinical deterioration, hypoxemia, right ventricular dysfunction, and acute lower extremity erythema or swelling. If any of these features are encountered, a low threshold for performing diagnostic imaging procedures should be implemented. Those include primarily CTPA to detect PE, and compression ultrasonography to diagnose DVT. Although less conclusive, especially in the case of unstable patients who cannot be transferred, echocardiography serves as an alternative to support the clinician´s suspicion. After confirmation of VTE, it is recommended to use established guidelines for the anticoagulative treatment of VTE. Parenteral anticoagulation with therapeutic weight adjusted LMWH serves as the first line therapy in hospitalized Covid-19 patients with VTE and absence of contraindications. While both LMWH and UFH lack known drug interactions with antivirals or investigational therapies compared to DOACs, LMWH is favored over UFH, because of routine monitoring with frequent blood draws in the case of UFH. Additionally, LMWH may not lead to heparin pseudo-resistance. Anticoagulation therapy should be continued for at least three months with administration of DOACs in the post-hospital discharge setting. In view of the outcome, one study demonstrated an increased risk of mortality in their Covid-19 cohort with DVT in relation to Covid-19 patients without (40.3% vs. 14.9%) (370) Data, which also analyzed DVT outcomes among a non-Covid-19 cohort showed comparable rates of mortality in relation to Covid-19 patients (17% vs. 19%). (371)

In contrast, Spirk et al. (372), who examined consecutive patients with acute VTE during a pre-Covid era, revealed lower rates of overall in-hospital mortality with 5.3%. One study which compared the mortality of PE, detected a significantly higher risk of in-hospital death in the Covid-19 cohort with 12.8% versus 5.3% in the non-Covid-19 group. (373)

5.2.4 Covid-19 associated cerebral venous thrombosis

The meta-analysis on the occurrence of CVT by Baldini et al. (374) included 57 cases with a mean age of 53.5 years. Although reported CVT rates vary, pooled data estimate a frequency of 0.08% (or 8 cases per 10,000) in patients hospitalized for Covid-19. This exceeded the anticipated rate of 5 per million in conventional cases. (356, 375) The proportion of CVT in cardiovascular events associated with Covid-19 was calculated to be approximately 4%. In the majority of patients, Covid-19 symptoms preceded CVT-related features with 90%. Typical neurological signs and symptoms were detected in every patient with CVT, with encephalopathy, focal signs, hemiparesis, or seizures as the main presenting complaints. (374) According to data from Al-Mufti et al. (376), 85% of CVT patients presented with headache as the most common symptom. Moreover, altered mental status frequently occurred, and epileptic seizures were noted in 28% to 42% of patients. Thereby, signs and symptoms seem to be equal to cases without SARS-CoV-2 infections. Analyses revealed transverse sinus as the most affected (65%), while the sigmoid sinus, and superior sagittal sinus revealed similar rates with around 45%. Thrombosis involved more often the deep venous system compared to cortical veins and multiple venous vessel involvement dominated over single vessel affection. (374, 376) Hemorrhagic lesions were detected in 42%. D-dimer and CRP levels were elevated in most cases across different studies, and lymphopenia predominated, when reported, in the meta-analysis. The diagnosis of CVT in Covid-19 does not differ from conventional diagnosis, as CT or MR venogram or CT-angiography were the first-line imaging techniques for the diagnosis of CVT. (374, 377) Additionally, CVT therapy in Covid-19 is similar to the treatment of CVT without infection, while no specific guideline was elaborated yet. (378) Compared to a cohort without Covid-19, in-hospital mortality was high with rates between 25-40% versus 6%, and especially parenchymal hemorrhage was associated with an adverse outcome. (374, 376, 379)

5.2.5 Covid-19 associated stroke

As mentioned above, stroke often complicates the course of Covid-19, with ischemic stroke ranking among the most common arterial thrombotic events. While results for ischemic stroke rates varied between 0.9 to 2% across hospitalized Covid-19 cohorts, the frequency rose among ICU patients (3-6%). (340, 350, 380-382) In comparison, studies on the in-hospital stroke rates among patients admitted because of influenza or for any other reason were lower, with 0.2% and between 0.04% and 0.06%, respectively. (383-386) The 7.6-fold increased odds for cerebrovascular events in relation to influenza illustrates the perceptible heightened risk of suffering from stroke during Covid-19. (385) Although less common than ischemic strokes in Covid-19, the proportion of hemorrhagic strokes is eventually higher than the distribution in non-Covid-19 cases (72:28% vs. 87:13%). (256, 387) In view of the typical features of Covid-19 associated ischemic stroke, previous reviews revealed a predominance of large vessel involvement over small vessel disease, which was present in only 2%. (380, 381) Instead, stroke databanks on preceding non-Covid-19 cohorts attribute 20% of stroke cases to small vessel disease. (388) Cryptogenic stroke rates are, in contrast, only merely elevated in Covid-19 cohorts compared to those without, with declared rates of 35 to >40%. (380, 381, 389) Vogrig et al. (381) detected multi-territory involvement, and involvement of otherwise uncommonly affected vessels as potential specific features of Covid-19 related stroke. Patients with Covid-19 and ischemic stroke typically present with severe neurological deficits, with median NIHSS values of 19-21, as compared to non-Covid-19 patients with a median of four. (381, 390) Of note, in one quarter of Covid-19 patients, ischemic stroke was associated with additional thrombotic events.

Neurological findings among 323 patients with concomitant SARS-CoV-2 infection and acute ischemic stroke revealed limb paresis as the most common symptom (>72%). (391) Altered level of consciousness, aphasia and facial paresis were additional frequently observed clinical features. Together with ataxia, gaze preference, visual field or sensory loss, the signs and symptoms of Covid-19 associated ischemic strokes appear to resemble those without known infection as quoted in the study by Yew et al. (392) This hypothesis is emphasized by several case reports, consolidated in the study by Ghasemi et al. (393) Different case series and comparative studies evaluated alterations of biomarkers in acute ischemic

stroke patients with Covid-19. The study by Strambo et al. (394) revealed a significantly prolonged aPTT, elevated CRP and decreased LDH levels, and D-dimer levels were 2-fold higher than in Covid-negative stroke patients. While data from Vogrig et al. (381) endorsed the laboratory features of increased coagulopathy, adding elevated fibrinogen, their cohorts exhibited higher LDH values. The limited existing data on the management approach to Covid-19 patients with suspected ischemic stroke follows the proceedings in established stroke guidelines. (395-397) CT imaging techniques are used for diagnosis and confirmed stroke cases are treated with systemic, intravenous fibrinolysis, and mechanical thrombectomy in selected patients. Studies which compared the treatment strategies between stroke patients with and without Covid-19 also showed no differences in the frequency of conducted intravenous thrombolysis or mechanical thrombectomy. (398) However, previous studies showed greater risks of post-rtPA intracerebral hemorrhage in patients with elevated CRP and D-dimer, which are typically increased in Covid-19. (399, 400) Moreover, the fact that rtPA is hepatically cleared and liver function tests are commonly elevated in Covid-19 patients, indicating liver dysfunction, may raise the risk of intracranial hemorrhage further. (381, 401) As in VTE, Simonetto et al. (400) recommended against decision making upon laboratory markers, such as thrombelastography or D-dimer levels. By contrast, the performance of mechanical thrombectomy in cases with large vessel occlusion is considered as safe and exhibits the same success rates compared to SARS-CoV-2 negative patients. (402) While studies on Covid-19 related stroke cohorts yielded deviating results in regard of the outcome in comparison to non-Covid-19 strokes, stroke significantly elevated the in-hospital mortality among Covid-19 patients (19.4% for Covid-19 and stroke vs. 6.2% for Covid-19 alone). (398, 403, 404) Further data from Qureshi et al. (398) attribute increased rates of cerebral edema, intracerebral hemorrhage and myocardial infarction in Covid-19 associated stroke patients compard to those without stroke. Additionally, Covid-19 and stroke lead to higher ICU admission rates and required intubation considerably more often when compared to stroke alone. (405) Moreover, patients had longer hospitalization rates, slower recovery, and unfavorable functional prognosis (modified Rankin Scale 4-6) in over 64% of cases according to a small case series by Hernández-Fernández et al. (406) with 17 SARS-CoV-2 positive ischemic stroke patients. In contrast, data from a pre-Covid

study showed unfavorable functional prognosis in about 15% of patients after three months. (407)

5.2.6 Covid-19 associated myocardial infarction

According to Jenner et al. (350), MI is the most common ATE in Covid-19 patients admitted to the ICU. However, after adjustment for cohort differences, MI hazard ratios were not significantly deviating from patients suffering from influenza, regardless of the medical care setting (in- and outpatients) in a study by Ward et al. (408) Data which compared MI incidences in hospitalized individuals with Covid-19 and a non-Covid cohort, supported these results by showing no considerable difference (2% vs. 2.5%). (409) With regard to the clinical features of ACS in Covid-19, Milovančev et al. (410) showed similar rates for STEMI, NSTEMI and angina pectoris compared to a non-Covid-19 cohort, with approximately 71%, 25%, and 3.6%, respectively. The North American COVID-19 Myocardial Infarction (NACMI) registry highlighted a higher prevalence of atypical STEMI symptoms in Covid-19, such as dyspnea and syncope rather than chest pain, in comparison to a historical STEMI cohort. (411, 412) The predominance of dyspnea is confirmed by the study of Kumar et al. (413), which showed rates of 68%. Still, chest pain as a typical MI symptom was also common with a reported rate of 60%. Covid-19 patients with ACS presented with a significantly but only slightly elevated heart rate (85 versus 80 beats/min). Additional data revealed that patients with ACS and Covid-19 experience higher rates of cardiogenic shock relative to patients with ACS alone, while cardiac arrest was comparable between the cohorts. (410, 411, 414-416) With 32%, heart failure was also more commonly detected in patients with concomitant SARS-CoV-2 infection and STEMI, compared to 18% in a STEMI cohort without infection. (412, 417) Garcia et al. (418) evaluated the change in clinical characteristics of Covid-19 patients with concomitant STEMI between 2020 and 2021. While typical ischemic symptoms with chest pain increased (51% vs 59%) in 2021, cardiac arrest rates before PCI remained comparable. The study also reported a trend towards lower cardiogenic shock rates. Of note, one study revealed significantly higher rates of very late STEMI presentation (>12h from symptom onset) in the Covid cohort compared to a control group. (410) Additional diagnostical findings featured typical ECG changes in all Covid-19 patients with MI and comparable EF among ACS patients with and without Covid-19. In the latter, a

reduced EF below 40% was reported in 25% of Covid-19 cases suffering from ACS. (410, 413) Analyses of coronary angiographies further revealed a substantially higher thrombus burden, elevated stent thrombosis rates, and greater incidence of multiple thrombotic culprit lesions. (419) While high-sensitivity troponin levels as well as NT-proBNP were significantly elevated in both included studies in patients with Covid-19 and STEMI compared to non-Covid-19 cohorts, they only tended to be higher in the study by Milovančev et al. (410) if all infected ACS cases were analyzed. (419) Contrary, LDH levels were significantly elevated compared to non-Covid-19 cases only in the study by Milovančev et al. (410) , while further laboratory parameters, such as fibrinogen, and ferritin were non-significantly elevated in Covid-19 patients with STEMI. Regarding the diagnosis and management of MI in Covid-19 cases, the guidance of the European Society of Cardiology states that the same ECG diagnostic criteria for all cardiac conditions also relate to Covid-19 patients. (420) Although, notable rises of cardiac troponin levels are often encountered in severe Covid-19 (indicating shock, respiratory failure, or hypoxemia) their measurement is also suggested in all cases with suspected MI. Additionally, according to a joint consensus statement, Covid-19 patients with signs of concomitant acute MI, including classic symptoms and ECG findings, might benefit from additional noninvasive imaging. (421) Both guidances therefore endorse the use of point of care ultrasonography to assess the cardiac function and aid in the detection of wall motion abnormalities. The results can further support a STEMI diagnosis and evaluate the merit of a fibrinolysis reperfusion. They also state that the same treatment approach as for non-Covid cohorts in terms of primary PCI is indicated (<120 minutes from diagnosis to reperfusion) in Covid-19 patients with STEMI. Urgent fibrinolysis in patients diagnosed with a STEMI at a referral hospital is also supported, with subsequent transfer for a rescue PCI where indicated. (421, 422) SARS-CoV-2 positive NSTEMI cases are also managed according to non-Covid cases, where urgent coronary angiography is only performed in the presence of very high-risk factors (<2 hours). Further acute MI therapies apply to the established guidelines for non-high risk NSTEMI and unstable angina. (421) When comparing STEMI treatments in cases with and without Covid-19, door-to-balloon times were markedly increased in infected individuals with more than eight minutes longer mean time compared to controls. (415, 423) Additionally, Covid-19 patients received primary PCI less often (71% vs. 93%). (411) While there were no significant

differences detected in regard of the PCI rates between Covid-19 STEMI patients in 2020 and 2021, door-to-balloon times improved in the latter. (418) In view of the outcome, all included studies revealed a significantly higher mortality in Covid-19 patients with acute MI or ACS in general, when compared to cohorts without Covid-19. (410, 415, 418) These results are exemplified by the aforementioned study from Garcia et al. (418), which showed a decline in mortality in Covid-19 patients with STEMI from 33% in 2020 to 23% in 2021, while the analyzed SARS-CoV-2 negative STEMI cohorts had rates of 14% and 11% in the same timeframe. In contrast, one study detected no significant differences in mortality when only NSTEMI cohorts were compared. (410)

5.2.7 Covid-19 associated acute limb ischemia

With rates between 0.2% to 0.9%, ALI is a rare finding among hospitalized patients with Covid-19. (347, 424) As mentioned above, the incidence of ALI is not significantly increased compared to the general population or a hospitalized influenza cohort, although designated data ascribe Covid-19 patients a trend towards elevated rates. (347, 348) These results are comparable with data from the United States, where a similar ALI prevalence in hospitalized Covid-19 and the general population was found (4 to 21 per 100,000 vs. 10 to 15 per 100,000) (425, 426) In the majority of included patients, ALI was diagnosed subsequently to SARS-CoV-2 infection, while 27% presented to hospital with ALI symptoms alone. (427) In accordance with ALI among the general population, lower extremity ischemia dominates over upper limb ischemia. (426) Compared to abovementioned data of non-Covid-19 ALI cohorts, femoro-popliteal arteries were most commonly affected with 45%, followed by tibial arteries, which were rarely involved in Covid-19 (222, 283, 428-430) Goldman et al. (431) found similar results with higher rates of Covid-19 associated thrombotic ALI in more proximal regions in comparison to SARS-CoV-2 negative patients, as well as a greater clot burden. Of the included studies, few stated the patients´ presenting complaints, signs and symptoms of ALI but ranked leg pain and discoloration to most frequent. Interestingly was the fact, that every Covid-19 patient with ischemic leg symptoms revealed also an arterial thrombus in leg arteries, compared to 69% in their control cohort. However, additional data in view of previous episodes of ischemia or arterial thrombi and examination findings were lacking. Still, it is assumed that patients with Covid-19 and ALI typically present

with the same symptomatology as the general population. (426) Regarding the severity of ALI in Covid-19 patients, the Rutherford classification with its required investigations is also used in individuals with Covid-19. Data revealed grades IIA and IIB as the most common in Covid-19 cohorts with concomitant ALI. (428-430, 432) Evidence from a pre-Covid-19 era coincide with these results, with two studies stating Rutherford IIB as the most common, followed by grade IIA. (433, 434) The European Society for Vascular Surgery (ESVS) analyzed whether Covid-19 patients should receive an adjusted management approach compared to ALI patients before the pandemic. (435) The recommendation to detect ALI with CTA or MRA remains valid, with the addition that complete imaging from the aortic arch to feet and hands is advised due to the aforementioned more extensive disease. The limited significance of laboratory markers in the diagnosis of ALI also relate to patients with Covid-19. Yet, data revealed that ALI occurrence is often signalized by rising D-dimer levels among hospitalized Covid-19 patients. (426, 435, 436) Following verified ALI diagnosis, the standard management approach also applies to Covid-19 patients, including the administration of UFH or LMWH. (435, 437) Open surgical and endovascular treatment options remain the definite therapeutic approaches. However, as hospitalized Covid-19 patients may suffer severe disease, they might benefit from endovascular techniques as a less invasive procedure. A systematic review by Galyfos et al. (438) in contrast, showed that medical treatment alone was implemented in >41% of included ALI patients with Covid-19 as the first-line therapy. This approach led, however, to increased mortality rates when compared to endovascular or open surgery treatments, while the risk of amputation remained non-significant between these cohorts. Moreover, studies declared that 14% to 23% of patients already received anticoagulation at the time of ALI diagnosis, but rethrombosis after revascularization occured despite full heparin-based anticoagulation. (430, 432, 439, 440) Regarding the outcome of interventions, the systematic review by Attisani et al. (427) revealed technical success in 68% of cases, while 13% required a re-intervention due to persistent or recurring limb ischemia and 17 out of 194 patients had to undergo amputation. In contrast, in the aforementioned pre-Covid cohort, preservation of the limb was ensured in 96%, if revascularization was successful within six hours of symptom onset. (203) Of note, 19% of Covid-19 patients with ALI were ineligible for surgical or endovascular procedures because of their poor clinical state. Amputation and mortality rates of

cohorts with concomitant Covid-19 and ALI ranged between 23.2% to 25% and between 29% to 38%, respectively. (431, 435, 438, 441) By comparison, between 3% to 8.9% of patients with ALI alone deceased. (431, 435, 441, 442) Additionally, mortality and amputations were decreased in patients who experienced symptoms limited to the leg, without other systemic or respiratory Covid-19 manifestations. (431)

5.2.8 Covid-19 associated vasculitides

Although numerous case reports describe certain vasculitides associated with Covid-19, only the most important entities are described in the upcoming paragraph. Presumably, the most prominent vasculitic feature of Covid-19 is endotheliitis, playing a central role in the above-described pathophysiology with its thromboembolic sequelae. However, precise epidemiologic data on the frequency of other Covid-19 associated vasculitides are mostly lacking, partly because they are rare findings. For Kawasaki-like vasculitis, available data estimate 316 cases per 1,000,000 in individuals younger than 21. Cutaneous vasculitis represents another frequently described phenomenon in Covid-19, and one case series revealed an incidence of 2.9%. Both usually occur in patients without severe Covid-19 pneumonia. (288, 289, 443, 444) Concerning the skin manifestations, the predilected sides include the dorsal aspects of the toes, called ‘Covid toes’. Interestingly, these chilblain-like lesions can occur throughout the course of Covid-19, as they had been reported before onset of disease, as well as weeks thereafter. In general, the management and treatment approach to cutaneous vasculitis in Covid-19 patients is scarcely described in the literature but included topical medication where mentioned. Additionally, the lesions typically resolved within a few weeks. (444) Furthermore, the spectrum of Kawasaki-like vasculitic patterns in Covid-19 patients predominates in younger individuals and is typically accompanied with MIS. However, coronary artery aneurysms or ectasia are less common compared to historic rates (10% vs 15-25%). (289, 445-447) In a study, which compared the clinical features of SARS-CoV-2 associated Kawasaki-like disease to a pre-outbreak KD control, gastrointestinal symptoms (abdominal pain, diarrhea, and vomiting), myocarditis, neurological signs, and serous effusions occurred more frequently in the former. Additionally, KD shock syndrome rates were more common in children and adolescents with Covid-19 and ICU admissions were increased.

Regarding laboratory markers, SARS-CoV-2 associated Kawasaki-like cases exhibited higher CRP and procalcitonin levels, as well as more serious lymphopenia, while platelet and fibrinogen levels were similar to classic KD. The treatment regimens did not differ between the cohorts, and all patients responded to intravenous immunoglobulin (IVIG) therapy. However, Covid-19 patients received more often additional corticosteroids in combination with IVIG. Patients in both groups had favorable outcomes, without deaths during their follow-up. (448) Other vasculitides are rare findings in Covid-19 patients, and data on large vessel vasculitis are limited to case reports. For example, a systematic review described no case of TAK in relation to Covid-19. (288) In addition, although ANCA are prevalent in a high percentage of hospitalized Covid-19 patients, genuine AAV cases are scarce in the literature. (288, 449) Moreover, IgA vasculitis may be correlated with Covid-19, but vasculitis arose more than one month after SARS-CoV-2 infection in some cases. The patients´ main complaints included purpuric rash and gastrointestinal symptoms and skin biopsies unveiled the typical leukocytoclastic vasculitis pattern. (450) Of interest is the finding that Goodpasture´s syndrome is a rare finding in Covid-19 patients, despite the involvement and damage of pneumocytes and the pulmonary basement membrane, which may induce autoimmunity with autoantibody production. (451, 452) However, further comprehensive data on the management approach and outcomes compared to patients without Covid-19 are lacking for the latter mentioned vasculitides so far.

6 Discussion

The aim of this review was to combine the pivotal pathomechanisms contributing to vasculopathies in Covid-19 and to highlight recent clinical aspects of major Covid-19 associated vasculopathies with focus on hospitalized patients.

Studies addressing the particular involvement of endothelial cells during Covid-19 endorse the hypothesis of a prevailing indirect response of the endothelium to adjacent epithelial infection rather than direct viral infection in vivo. In summary, the investigations emphasize the crucial role of endothelium during severe Covid-19 ranging from active release of pro-inflammatory cytokines to apoptotic cell death, and highlight endotheliitis as a specific feature. In addition, endothelial dysfunction plays a key role in the pathogenesis of severe Covid-19 and both direct infection and indirect activation of endothelial cells contribute to subsequent progression of a

systemic microcirculatory dysfunction. Since high viral titers are necessary to infect endothelium in vitro, additional research is required to determine the exact viral load in the lower respiratory tract in relation to disease severity and patient outcomes. Likewise, neither study investigated the time course between pneumocyte decay and subsequent infection of endothelial cells, as direct endothelial invasion was proven in some autopsy studies and in vitro models. However, if endothelial involvement is in fact restricted to indirect mechanisms without direct infection with SARS-CoV-2, the question remains when endothelial cells induce apoptosis in the course of disease. Either way, these pathomechanisms could enable the virus to gain access to the vasculature followed by dissemination into additional vascular beds and organs. However, Varga et al. and Schimmel et al. (290, 296) only presented small case numbers, which limits the significance derived from their results.

Immunothrombosis, as another key pathophysiologic mechanism in Covid-19, represents a physiological, complex process of intense immunologic as well as thrombotic activation in which both systems are mutually stimulated to efficiently kill and block the spread of pathogens. The result is a microthrombus, consisting of high amounts of fibrin, platelets, neutrophils with NETs, and monocytes/macrophages with trapped virus particles. Under normal circumstances, this allows pathogen killing limited to the intravascular space without exaggerated reactions or collateral organ damage. At the same time, unrestricted immunothrombosis might lead to detrimental effects with formation of microthrombi throughout the host´s vascular beds, similar to DIC as seen in sepsis. (306) Therefore, immunothrombosis also allows the explanation of severe complications aggravating the course of disease, including the hyperinflammatory state, ARDS and Covid-19-associated coagulopathy. However, the precise pathomechanisms or triggers leading to this dysregulated immunothrombosis in severe Covid-19 remain elusive. Additional research is therefore necessary to uncover the missing link between a protective immune reaction and exaggerated microthromboses. Thus, adequate therapeutic measures to restrain immunothrombotic sequelae and novel treatment options might be implemented. The partially inconclusive results of RAS imbalances in Covid-19 associated vascular dysfunctions by Pucci et al. (317) require additional data to unveil the true impact of RAS alterations. Especially, changes in the

proportion of membrane ACE-2 to soluble ACE-2 in the plasma warrants further investigation, as well as the explicit consequences after binding SARS-CoV-2.

With respect to the identification of surrogates indicating endothelial dysfunction and activation of systems involved in the immunothrombotic process, the combination of data revealed promising biomarkers. Besides reflecting the intravascular mechanisms during severe Covid-19, they can also serve as markers to predict patients´ outcomes, inclusive of mortality. Especially D-dimer levels, sTM and vWF:Ag were associated with disease severity and mortality prediction. Albeit their important findings, the studies contain considerable limitations. In most cases, patients received heparinization or other drugs to restrict the procoagulatory state and reduce inflammation, which could impact the results of several biomarkers measured in the trials. Moreover, disease severity definitions varied between studies, as different categorization tools were used or study specific categories were implemented, making comparisons of studies difficult. Therefore, larger prospective trials are necessary to further evaluate the proposed markers and compile an appropriate prediction model for Covid-19 severity and its outcomes. Thereby, therapeutic algorithms might be developed to promptly intervene with specific therapies and avert aggravating complications. Studies on platelet activation and its specific biomarkers are also warranted, as well as continuous studies regarding the sustained endothelial activation in convalescent individuals. As indicated above, a potentially misleading study approach, is the use of convalescent plasma samples. In the study by Sinkovits et al. (328), which showed decreased ADAMTS13:Ac and elevated vWF:Ag in Covid-19 patients, data were expressed as the percentage relative to the values of convalescent controls. This might be relevant in the case of prolonged plasma levels outside the normal range after clinical recovery, since no ADAMTS13:Ac below 10% was measured. This threshold marks the transition to severe ADAMTS13 deficiency, which in turn is a relatively specific finding in TTP. (453) To conclude, if convalescent controls exhibit sustained diminished ADAMTS13:Ac levels, measurements in the Covid-19 cohort were false high and values of <10% could have occurred.

Studies on NETosis and NET formation support their essential impact in the development of exaggerated immunothrombosis. In particular, severely affected patients suffer from uncontrolled NETosis with elevation of specific biomarkers measurable in the patients´ serum and plasma. The results are indicative of

intensified NET production in combination with diminished NET clearance, leading to microvascular damage and thrombosis, typical for immunothrombosis and severe disease. The positive correlation between neutrophil count and NET-markers is reasonable, given the fact that neutrophils represent the common source of NETs. Moreover, the correlations with surrogates indicative of inflammation (CRP, TNF-α and IL-6) and a procoagulant state (D-dimer) again support the synergy of these systems in severe Covid-19 and thereby the predominant pathomechanisms explained by immunothrombosis. Potential connections between ongoing endothelial dysfunction and NETosis were also evaluated by different study groups. In conjunction with the specific NETosis markers, the studies of Fogarty et al., Middleton et al. and Ng. et al. (324, 336, 337) indicate that ongoing endothelial cell activation and damage is irrespective of NETosis. Considering the preliminary findings, additional trials are warranted to detect potential pathways which sustain endothelial dysfunction in convalescent patients. Thus, new treatment approaches to prevent ongoing microangiopathy and its consequences might be developed. Several potential treatment approaches and new agents have been described in vitro experiments to attenuate NETosis and degrade NETs and ongoing trials evaluate their safety and efficacy in humans. Further data evaluating the competence of LMWH accelerating NET degradation similar to UFH are needed in the development of future therapy regimens. Patients could benefit from combinations of DNases with LMWH by unifying anticoagulant properties with optimized NET clearance. By this means, micro- and macrovascular thrombus formation might efficiently be decreased, especially in severely affected Covid-19 patients. Hence, treatment of Covid-19 patients with heparins could also influence NET parameters, leading to distorted laboratory measurements. Nevertheless, additional studies are necessary to understand the chronology of NETosis induction and immunothrombosis to specifically disrupt the cascade of inflammation and coagulation at various levels. Prospective studies could verify the observation that certain NET-biomarkers might serve as prognostic indicators and thereby also influence the therapeutic approach.

Despite their valuable contributions to elucidate the involvement of NETosis and NETs in immunothrombosis and severe Covid-19, the studies also contain limitations. A few studies did not mention the therapeutic regimens in their Covid-19 cohorts, complicating the comparability of different studies. As mentioned above,

heparin treatment before blood draw could potentially affect NET-marker concentrations. However, neither study compared NET surrogates before and after administration of heparins or anticoagulants in general. Therefore, future trials should evaluate their impact on NETosis in vivo, and assess synergistic effects with additional agents. Another limitation regarding the comparability of the trials is the different Covid-19 severity scales used to classify hospitalized patients into moderate, severe, or critical cohorts. While some studies used prespecified guidelines, which also diverge, others solely differentiated according to the patients´ respiratory requirements (ambient air vs. mechanical ventilation). Due to the small number of autopsy samples, ranging from three to eight cases, the results of these NETosis studies are of limited significance. Nevertheless, structures and markers of NETs were identified within microthrombi in decedents. One study refrained to provide information about the healthy control cohort, including their number, convalescence status or if they were matched to sex and age.

To conclude the epidemiology of thromboembolisms during Covid-19, these events are frequently observed complications among hospitalized Covid-19 patients. Most notably, their frequency rises with disease severity and thereby peak in patients admitted to the ICU. Although partially inconclusive results, when comparing the risk of VTE between Covid-19 patients and the general hospitalized population, reported data from ICU cohorts attribute Covid-19 patients a significantly higher risk for VTE, and PE in particular. In contrast, reported incidences of ATE are comparable between hospitalized patients with and without Covid-19. In general, VTE typically occurs more often than ATE across all hospitalized cohorts. Only the included study by Bilaloglu et al. (349) revealed more ATE than VTE cases. The markedly increased prevalence of MI with 8.9% in hospitalized patients might be partly explained by the search method, a natural-language processing tool, which searched for eligible patient records. This could have led to the inclusion of suspected but not confirmed MI cases as well as patients with isolated troponin elevations. This presumption is emphasized by the results of Jenner et al. (350) which included this cohort study to report the incidence of ATE within Covid-19 patients admitted to the ICU. The authors suggested that early reports often classed a troponin rise in Covid-19 patients with myocardial infarction, instead of attributing the finding to the more common non-ischemic myocardial injuries. The authors of the paper on the ATE incidences pointed out that significantly more Covid-19

patients received thromboprophylaxis, thereby potentially biasing the ATE rates of this cohort. (348) Of interest is the finding that PE rates were comparable to DVT in some studies, suggesting a role of in-situ pulmonary thrombi. Together with the increased intrapulmonary microthrombi found in histopathologic samples and the presumed pathomechanisms including immunothrombosis, the finding of DVT-independent PE might reflect a specific feature of Covid-19. The considerably lower incidence of VTE in the retrospective study by Roberts et al. (342), compared to the data of the included meta-analyses, could derive from the deviating stages of the pandemic from which patients were recruited to the studies. While patients included in the meta-analyses had been hospitalized before September 2020, the observational study of Roberts et al. (344) enrolled patients between March 2020 and March 2021. Another explanation may be the administered thromboprophylaxis. Early in the pandemic, the prothrombotic traits of Covid-19 were widely unexposed and a minor percentage of hospitalized patients received anticoagulation. In conjunction with accumulating evidence of frequent thromboembolic events, the institution of anticoagulation has become a cornerstone in the therapy of hospitalized individuals. The finding of declining detection rates over the course of the pandemic could thereby reflect the efficacy of anticoagulation among generally improving treatments.

Another remarkable finding is the significant increase in detection rates of VTE determined by a systematical screening approach in contrast to testing upon suspicion. This improved VTE diagnosis in screened Covid-19 patients might also impact the current diagnostic approach and management algorithm of hospitalized patients. However, literature on the benefits of systematical screening of hospitalized patients regarding outcome and survival is scarce, and neither of the cited studies reported such information. To date, different guidelines do not recommend routine screening for DVT in hospitalized Covid-19 patients without signs indicative of VTE. (454, 455) While early clinical guidance pronounced against routine screening for VTE, the guideline of the National Institutes of Health awaits additional evidence before recommending either for or against this strategy. (369) Regarding the discovered risk factors for thromboembolic events, elevated levels of D-dimer at admission, male gender, and cancer were commonly stated, whereas hypertension and diabetes did not reveal significant correlations in Covid-19. In this context, it is noteworthy that the distribution of ethnicities in the incorporated studies

was not representative of the global community. The impracticality of generalizing the obtained incidences and risk factors is strengthened by the Chinese multicenter study, which detected VTE in only 1.5% of hospitalized patients. (353) Race-related differences in thrombotic risk, however, were already indicated before the current pandemic and demonstrated the lowest rates in Asians and Pacific Islanders. (456) These racial disparities also seem to relate to Covid-19, given the results of an elevated risk for Black ethnicity and the low VTE rates among a Chinese patient population. Nevertheless, the high rates of VTE, despite administration of at least prophylactic doses of anticoagulants, are remarkable. Several trials have therefore already been conducted, and additional studies are currently carried out to ascertain the optimal anticoagulative prophylaxis and treatment. Subsequent trials and research are required to reveal the proportion of intrapulmonary thromboses in the development of PE and thereby pave the way for specific treatment options. Future studies are further warranted to assess the effects of systematic screening compared to testing on clinical suspicion, with special emphasis on outcome and survival. Those should systematically evaluate racial disparities in the setting of thromboembolic events.

The studies´ findings on the context of Covid-19 and thrombotic events impact the further management and treatment of hospitalized patients. Still, the gained knowledge is subject to limitations. Despite comparable groups, regarding age, gender, and method of diagnosis, the inferior quality of evidence originates from significant heterogeneity among the incorporated studies. Meta-analyses primarily relied on observational studies that were retrospective in the majority, which possibly under-estimated the incidences of thrombotic events. Additionally, the included studies exhibited considerable methodological differences. For instance, Tan et al. (340) demonstrated higher VTE detection rates among multicentric series with larger cohorts, than monocentric series with smaller cohorts, which underlines the heterogeneity of incorporated studies. The differences in declared incidences become particularly comprehensible when the two diagnostic strategies of either systematical screening or symptomatic testing are compared. Moreover, all studies solely declared the all-cause mortality in their patient cohorts with and without thromboembolisms, rather than the specific cause of death, especially due to any thrombotic event. Albeit death is associated with thromboembolisms, the conclusion that those directly lead to death cannot be drawn and warrants further research.

Moreover, data on the incidences of ATE are scarce, especially in terms of comparisons between Covid and non-Covid-19 cohorts and additional prospective studies are required, which precisely distinguish between the single entities (i.e. MI, stroke, ALI and mesenterial ischemia).

The high burden of venous thrombotic complications in Covid-19 becomes particularly obvious when comparing affected hospitalized patients with non-Covid-19 cohorts. VTE rates among Covid-19 patients admitted to the ICU are significantly higher than in the general ICU population, which also relates to PE rates when compared to influenza H1N1, SARS, or MERS. Although less frequent in Covid-19, also CVT rates are higher compared to the previously described prevalence. These results attribute moderate to severe SARS-CoV-2 infections again a high potential of thrombogenicity and further prove the truly elevated risk for VTE in hospitalized Covid-19 patients, especially in ICU cohorts. Regarding the symptomatology, the included studies revealed similar signs and symptoms for VTE and CVT, without stating potentially Covid-19 specific manifestations, compared to non-Covid-19 thrombotic events. This is especially challenging regarding the diagnosis of PE, as PE and Covid-19 associated pulmonary symptoms often overlap. Noteworthy is the finding that segmental and subsegmental PE are the dominating locations in Covid-19, contradicting the results of García-Sanz et. al. (361), which detected primarily central PE in a pre-Covid era. Nevertheless, mortality rates are increased in this patient cohort with segmental PE and Covid-19, also in comparison to segmental PE in the absence of Covid-19. These observations could further endorse the hypothesis of in-situ pulmonary thrombosis occurring to a considerable extent, rather than emboli originating from DVT. Despite deviating results concerning the predominantly observed location of DVT, the higher prevalence of distal thrombi in Covid-19 might again derive from the procoagulant state due to unrestrained immunothrombosis. With reference to significant biomarkers, the degree of D-dimer elevation indeed indicates a higher risk of thrombotic complications and mortality in Covid-19, yet the parameter is not applicable for the diagnosis of VTE. Although D-dimer levels are highly increased in VTE patients and thereby represent a robust marker, the fact that also severe Covid-19 cases without thromboembolisms might exhibit substantially augmented values, limits its significance. The same applies to the detected elevated levels of D-dimer, as well as CRP in CVT. At present, specific cut-off values are lacking to discriminate between severe Covid-19 and actual VTE

or CVT cases. In combination with advanced, Covid-19 tailored VTE and DVT assessment scores, implemented D-dimer levels could aid in their diagnosis among hospitalized patients with Covid-19. Guidelines on VTE diagnosis and treatment regimens are mainly in accordance with already established guidelines in this field. However, a CVT specific guidance in Covid-19 is still missing, which is at least partly caused by the lack in prospective studies and current meta-analyses. Regarding VTE, no systematic screening approach is advised in hospitalized Covid-19 patients to date, and further imaging procedures should be based upon clinical suspicion, rather than changes in biomarkers. However, a low threshold to perform these procedures is appropriate, especially if any symptoms indicative of VTE occur. In contrast to the established guidelines, LMWH represents the sole primary anticoagulant in Covid-19 in most cases, as UFH and DOACs feature unfavorable side effects or evitable drug interactions. While VTE deteriorate the overall outcome in Covid-19 patients, only PE seems to increase the risk of mortality compared to non-Covid-19 cases. In contrast, mortality in cases with CVT and Covid-19 is significantly worse than in individuals without infection. The incorporated management and treatment guidelines for VTE of the “CHEST” panel and “International Society on Thrombosis and Haemostasis” were both developed during 2020, when the first subtype of SARS-CoV-2 spread across the globe. At that time, less was known about the procoagulant state in hospitalized patients, as well as its underlying pathophysiology including immunothrombosis. Therefore, their recommendations could be outdated, also in regard of the differences between evolved SARS-CoV-2 strains, and contemporary, Covid-19 specific VTE guidelines are highly warranted. This not only applies to the therapeutic approach but also the management strategies, including imaging procedures. As in-situ pulmonary thrombosis constitutes a frequent finding, and small- to medium-sized pulmonary arteriole and venule thromboses are often described, special attention should be drawn on these regions, when assessing CTPA. (289)

While literature on the epidemiology of VTE in Covid-19 vs. non-Covid-19 cohorts is available, data on the symptomatology of VTE are limited. As one of the studies´ limitations, the cohorts mainly consisted of small groups in most of the included papers. Data from the RIETE registry, as one of the few studies to specify PE associated symptoms in Covid-19, only included 379 patients. Details on symptomatic DVT were even scarcer. Thus, derived classic symptoms indicating

VTE in Covid-19 are less conclusive and remain at least partially unknown. Furthermore, data on the typical locations of DVT arose from small study groups (<150 patients). Despite available data on the epidemiology and symptomatology of CVT, these studies based on even smaller patient numbers, with the largest cohort consisting of 57 cases in the meta-analysis by Baldini et al. (374) Other incorporated studies included the clinical features of solely eight to twelve patients. This is partly caused by the lower prevalence of CVT compared to VTE in Covid-19. Thus, a current meta-analysis, which gathers the detected clinical features of CVT in Covid-19 during the pandemic is warranted, as the included meta-analysis included cases until December 2020. Thereby, a more comprehensive guideline on the management and therapy of CVT could be implemented. As comprehensive data on many aspects of Covid-19 associated VTE and CVT are still lacking or are limited due to small case counts in the literature, additional trials and studies are warranted to fill the gaps. With the aid of prospective studies and meta-analysis, further evidence of the common and potentially specific signs and symptoms of VTE and CVT could be obtained. In addition, the gathered knowledge to optimize management and treatment regimens needs to be included in updated guidelines, to improve patient outcomes and survival, especially in the cohort of hospitalized patients with Covid-19 and VTE or CVT. Additionally, meta-analyses on the risk of mortality, which incorporate Covid-19 and non-Covid-19 cohorts and post-mortem studies, may illuminate the true mortality attributable to VTE. Furthermore, inclusion of larger cohorts to analyze the outcome and mortality of CVT in Covid-19 could lead to more reliable results compared to the incorporated highly varying mortality rates (25-40%).

Although generally less common than VTE, ATE tremendously impact the course of disease in Covid-19, especially in hospitalized patients. While the rates of acute MI and ALI are not significantly elevated in Covid-19 compared to a control cohort, stroke incidences are markedly higher in contrast to influenza or the general in-hospital patient population. It seems that ischemic strokes in Covid-19 patients are also more severe compared to non-Covid-19 cohorts, and incidences rise with Covid-19 severity. This is highlighted in the study by Vogrig et al. (381) showing the highest rates in patients admitted to the ICU. However, as the knowledge on the occurrence of ATE and hypercoagulability in Covid-19 evolved, also the clinicians´ awareness of recognizing their specific features increased. Thereby, strokes might

have been detected more frequently, especially among ICU cohorts. On the other hand, implementation of routine thromboprophylaxis could have prevented additional strokes during advanced stages of the pandemic, which also relate to MI and ALI. Regarding the potential cryptogenic stroke in Covid-19, immunothrombosis derived in-situ thrombosis and vasculitis may also contribute to its pathogenesis. Covid-19 associated stroke and ALI symptoms seem to be similar to cases without Covid-19, but the current literature is scarce on specific signs or details on their frequency. Therefore, due to the studies by Shahjouei et al. (391), Yew et al. (392) and Goldman et al. (431), which included only small cohorts, it can be only assumed that Covid-19 related stroke or ALI feature the same symptoms as in non-Covid-19 cases. In MI cases, atypical symptoms were common, especially early in the pandemic, but besides dyspnea, typical chest pain was also frequently described in Covid-19 patients. However, in regard of the data of the NACMI, which also showed a higher frequency of pulmonary infiltrates, the resulting respiratory symptoms of Covid-19 could also mask or superpose the typical red flags of MI. (411) For example, like in PE, shortness of breath is also a common finding in Covid-19 without MI, and also chest pain might constitute a presenting complaint in Covid-19 patients without ACS. In contrast to Covid-19 associated STEMI characteristics, data on the symptomatology of NSTEMI in Covid-19 patients were barely found in the literature.

The analysis of altered biomarkers in Covid-19 associated ATE partly showed significant distinctions to patients without Covid-19. However, as these markers are also commonly elevated in Covid-19 patients without confirmed ATE, their reliability is limited. Thus, a specific indicating parameter for the different ATE is arguably unavailable in Covid-19, except for D-Dimer. While the general diagnostic approach to ATE is assumed to be eligible for Covid-19 patients, specific future guidelines on the treatment may deviate from the current. Especially regarding the higher risk of intracerebral hemorrhages after administration of rtPA in the case of commonly elevated biomarkers in Covid-19, and compromised liver function. While data attribute Covid-19 patients with concomitant MI or ALI a significantly increased mortality, the results on the risk of mortality in stroke patients with and without Covid-19 were inconclusive. However, the detection of increased rates of cerebral edema, intracerebral hemorrhage, and myocardial infarction by Qureshi et al. (398) could partly explain the significantly heightened risk of mortality in their cohort with stroke

and Covid-19, compared to those with Covid-19 alone. Functional prognosis seems to be worse in Covid-19 patients with stroke compared to stroke alone, however these data based only on a small SARS-CoV-2 positive cohort. (406)

Similar to VTE, also studies on the characteristics of ATE in Covid-19 cohorts are subject to limitations, mainly due to small patient number or inclusion of data from case reports. Findings from Milovančev et al. (410) on the rates of the different ACS were based on 83 hospitalized Covid-19 patients, and compared with 166 non-Covid-19 individuals. Also the included studies by Choudry et al. (419), Strambo et al. (394) and Kumar et al. (413) on the symptoms and laboratory markers in Covid-19 patients with ATE included less than 40 patients. Furthermore, the reported features of ALI in Covid-19 originated from a study which only included 16 patients. (431) Moreover, with the exception of the paper by Garcia et al. (418), many comparisons between Covid and non-Covid cohorts were obtained from different time points, with results for the latter commonly originating from a pre-Covid era. As the pandemic influenced the entire health care systems around the world, and patients without SARS-CoV-2 infection avoided to seek help despite medical necessity, this could also impact the clinical presentation of non-Covid associated ATE. These comparisons are further limited, as studies from different time points during the pandemic were included. While some studies included patients during the first half of 2020, others reported data from patients hospitalized in 2021. (396, 405, 418, 419) Also the integrated meta-analysis mainly included retrospective observational studies, and the different sample size could have led to inherent selection bias, as stated in the analysis by Luo et al. (380) This also relates to the recommendations on ALI management and treatment in Covid-19 of the ESVS, who primarily incorporated data from case reports or small case series and only one randomized controlled trial. (435)

Overall, compared to VTE, Covid-19 associated ATE are less investigated, possibly due to their lower incidence in Covid-19. Nevertheless, their dramatic consequences warrant larger comparative studies, also to recognize rare but potentially specific signs and differences to conventional ATE. In particular, analyses of biomarkers in Covid-19 patients who experience arteriothrombotic complications are scarce, necessitating additional, well-designed studies with appropriate patient numbers. Additionally, the gap of Covid-19 associated NSTEMI features in the literature needs to be filled regarding the clinical picture and management. Eventually, the lack of

available studies in view of a Covid-19 adjusted therapeutic approach in ATE management, makes further, reliable studies essential. Especially, the availability of data concerning the administration of systemic fibrinolysis is poor and needs to be evaluated further, as fibrinolytic mechanisms are severely affected but poorly understood in Covid-19. (457) In addition, little is known about the functional outcomes in ATE patients in comparisons to non-Covid cohorts, particularly in the case of MI.

Aside from endotheliitis, which might be present in many severe Covid-19 cases, only Kawasaki-like disease and the cutaneous manifestations are better described Covid-19 associated vasculitides, with data also available on their epidemiology. While cutaneous vasculitis seems to be associated with mild courses and spontaneous resolution, Kawasaki-like disease tends to be more severe in association with Covid-19, as more patients required IVIG in combination with corticosteroids. However, additional studies are necessary, also to reveal the burden of long-term sequelae, especially in view of cardiac complications. Respecting the various other vasculitic entities, the included studies are primarily based on small case reports or series, and the correlation between these and Covid-19 need to be clarified. Despite the high prevalence of different autoantibodies during SARS-CoV-2 infections, their impact in triggering established autoimmune vasculitides needs to be further elucidated, but seems to be low so far. Again, the patient numbers of included studies were too small to allow general statements regarding the optimal Kawasaki-like disease treatment approach or its specific clinical features, as the study by Toubiana et al. (448) only included 23 Covid-19 associated patients and 59 from a pre-pandemic era. Therefore, further studies with greater patient numbers are warranted to enlighten the actual consequences of Covid-19 on the development of vasculitides.

The strength of this review is to provide comprehensive insights into the pathophysiological aspects of Covid-19 associated vasculopathies, including a compilation of potential biomarkers, and thereby also enables planning future studies. Moreover, it illuminates the occurrence of and differences between Covid-19 related vasculopathies and patients without SARS-CoV-2 infection in regard of their epidemiology, clinical characteristics, management, and treatment approaches. Thus, important knowledge gaps could be detected, which lead to future research questions to optimize Covid-19 specific guidelines and regimens.

However, the thesis is also subject to limitations. The review was not systematically conducted, therefore important papers and research data might not be included. Furthermore, not all databases were scoured, and additionally to the limitations of the incorporated studies, the data originate from different virus waves and variants of the pandemic. Therefore, differences between the potential variant-specific characteristics are unknown and may affect the rate and severity of vasculopathies. Finally, new emerging virus variants may have other impact on the clinical characteristics of vascular sequelae in Covid-19.

6.1 Conclusion

This review describes and combines the various interacting pathomechanisms leading to Covid-19 associated vasculopathies. The complex interaction of endothelial cells, immune and coagulation system, with NETosis and immunothrombosis as key promotors of Covid-19 associated vasculopathies, represents starting points for future management and treatment approaches. The fact that many laboratory markers are also commonly altered in severe Covid-19 cases impairs their significance for diagnosis of vascular complications. Covid-19 associated VTE and stroke seems to occur more frequent in hospitalized Covid-19 patients compared to non-Covid-19 patients. Additionally, a myriad of Covid-19 related vasculitides have been reported, while an actual correlation is only presumed in a few, in particular Kawasaki-like disease and cutaneous vasculitis. The management and treatment approaches are similar to those of conventional guidelines with only minor changes. Finally, mortality is elevated in most entities when compared to patients without Covid-19.

7 References

1. Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. Nature Reviews Microbiology. 2021;19(3):141-54.
2. McIntosh K. COVID-19: Epidemiology, virology, and prevention 2021 [updated 9.6.21. Available from: https://www-1uptodate-1com-1wwbz63ry065f.han.medunigraz.at/contents/covid-19-epidemiology-virology-and-prevention?search=undefined&source=covid19_landing&usage_type=main_section.
3. McIntosh K. Coronaviruses 2021 [updated 11.6.21. Available from: https://www-1uptodate-1com-1wwbz63ry0c44.han.medunigraz.at/contents/coronaviruses?sectionName=VIROLOGY&search=undefined&topicRef=126981&anchor=H2&source=see_link#H2.
4. Robert Koch Institute. SARS-CoV-2: Virologische Basisdaten sowie Virusvarianten 2022 [updated 15.07.2022. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Virologische_Basisdaten.html;jsessionid=53A4210A977FCDC66FC3641D2C3F4EF9.internet102?nn=13490888#doc14716546bodyText5.
5. Holmes EC, Goldstein SA, Rasmussen AL, Robertson DL, Crits-Christoph A, Wertheim JO, et al. The origins of SARS-CoV-2: A critical review. Cell. 2021;184(19):4848-56.
6. World Health Organization. WHO-convened global study of origins of SARS-CoV-2: China part: World Health Organization; 2021.
7. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020;182(4):812-27.e19.
8. World Health Organization. SARS-CoV-2 Variants of Concern and Variants of Interest 2021 [updated 15.6.21. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.
9. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538).
10. Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;593(7858):270-4.
11. Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 2020;182(5):1295-310.e20.
12. Calistri P, Amato L, Puglia I, Cito F, Di Giuseppe A, Danzetta ML, et al. Infection sustained by lineage B.1.1.7 of SARS-CoV-2 is characterised by longer persistence and higher viral RNA loads in nasopharyngeal swabs. Int J Infect Dis. 2021;105:753-5.
13. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv. 2020; [epub ahead of print].

14. Zahradník J, Marciano S, Shemesh M, Zoler E, Chiaravalli J, Meyer B, et al. SARS-CoV-2 RBD in vitro evolution follows contagious mutation spread, yet generates an able infection inhibitor. bioRxiv. 2021; [epub ahead of print].
15. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592(7855):616-22.
16. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-5.
17. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.
18. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021;372(6544):815-21.
19. Motozono C, Toyoda M, Zahradnik J, Ikeda T, Saito A, Tan TS, et al. An emerging SARS-CoV-2 mutant evading cellular immunity and increasing viral infectivity. bioRxiv. 2021; [epub ahead of print].
20. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. Microorganisms. 2021;9(7).
21. Hirabara SM, Serdan TDA, Gorjao R, Masi LN, Pithon-Curi TC, Covas DT, et al. SARS-COV-2 Variants: Differences and Potential of Immune Evasion. Front Cell Infect Microbiol. 2022;11:781429-.
22. Sheikh A, Robertson C, Taylor B. BNT162b2 and ChAdOx1 nCoV-19 Vaccine Effectiveness against Death from the Delta Variant. N Engl J Med. 2021;385(23):2195-7.
23. Scobie HM, Johnson AG, Suthar AB, Severson R, Alden NB, Balter S, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status - 13 U.S. Jurisdictions, April 4-July 17, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(37):1284-90.
24. Callaway E. Heavily mutated Omicron variant puts scientists on alert. Nature. 2021;600(7887):21.
25. Wang L, Cheng G. Sequence analysis of the emerging SARS-CoV-2 variant Omicron in South Africa. J Med Virol. 2022;94(4):1728-33.
26. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England; Technical briefing 31 2021 [updated 10.12.21. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042367/technical_briefing-31-10-december-2021.pdf.
27. Schmidt F, Muecksch F, Weisblum Y, Da Silva J, Bednarski E, Cho A, et al. Plasma neutralization properties of the SARS-CoV-2 Omicron variant. medRxiv. 2021.
28. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis. 2022;116:38-42.
29. World Health Organization. Statement on Omicron sublineage BA.2 2022 [updated 22.2.22. Available from: https://www.who.int/news/item/22-02-2022-statement-on-omicron-sublineage-ba.2.

30. World Health Organization. Tracking SARS-CoV-2 variants 2022 [updated 11.08.2022. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.
31. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions 2021 [updated 22.6.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Consequence.
32. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020 2020 [updated 11.2.20. Available from: http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020.
33. World Health Organization. Timeline: WHO's COVID-19 response 2020 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#event-16.
34. Fisher D, Heymann D. Q&A: The novel coronavirus outbreak causing COVID-19. BMC Medicine. 2020;18(1):57.
35. World Health Organization. WHO Coronavirus (COVID-19) Dashboard 2022 [updated 20.09.2022. Available from: https://covid19.who.int.
36. Adam D. The pandemic's true death toll: millions more than official counts. Nature. 2022;601(7893):312-5.
37. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern Med. 2020.
38. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396(10247):313-9.
39. Amboss. Covid-19 2021 [updated 21.6.21. Available from: https://next.amboss.com/de/article/gG0FAh#emWxeN0.
40. He W, Yi GY, Zhu Y. Estimation of the basic reproduction number, average incubation time, asymptomatic infection rate, and case fatality rate for COVID-19: Meta-analysis and sensitivity analysis. J Med Virol. 2020;92(11):2543-50.
41. Ortolan A, Lorenzin M, Felicetti M, Doria A, Ramonda R. Does gender influence clinical expression and disease outcomes in COVID-19? A systematic review and meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020;99:496-504.
42. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020;323(18):1775-6.
43. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021;174(1):69-79.
44. Liu L, Li Y, Nielsen PV, Wei J, Jensen RL. Short-range airborne transmission of expiratory droplets between two people. Indoor Air. 2017;27(2):452-62.
45. Association for Aerosol Research. Positionspapier der Gesellschaft für Aerosolforschung
zum Verständnis der Rolle von Aerosolpartikeln beim SARS-CoV-2 Infektionsgeschehen. Leibniz-Institut für Troposphärenforschung. 2020.
46. van der Valk JPM, In 't Veen J. SARS-Cov-2: The Relevance and Prevention of Aerosol Transmission. J Occup Environ Med. 2021;63(6):e395-e401.
47. Hamner L, Dubbel P, Capron I, Ross A, Jordan A, Lee J, et al. High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice - Skagit County,

Washington, March 2020. MMWR Morbidity and mortality weekly report. 2020;69(19):606-10.
48. Xiao F, Sun J, Xu Y, Li F, Huang X, Li H, et al. Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19. Emerg Infect Dis. 2020;26(8):1920-2.
49. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. 2020;323(16):1610-2.
50. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020 [updated 16.2.20. Available from: http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.
51. Leblanc J-F, Germain M, Delage G, O'Brien S, Drews SJ, Lewin A. Risk of transmission of severe acute respiratory syndrome coronavirus 2 by transfusion: A literature review. Transfusion. 2020;60(12):3046-54.
52. Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. Bjog. 2020;127(11):1324-36.
53. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. Science. 2021;371(6525):172.
54. Kiros M, Andualem H, Kiros T, Hailemichael W, Getu S, Geteneh A, et al. COVID-19 pandemic: current knowledge about the role of pets and other animals in disease transmission. Virology Journal. 2020;17(1):143.
55. Elias C, Sekri A, Leblanc P, Cucherat M, Vanhems P. The incubation period of COVID-19: A meta-analysis. International Journal of Infectious Diseases. 2021;104:708-10.
56. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic. Annals of Internal Medicine. 2021;174(5):655-62.
57. Qiu X, Nergiz AI, Maraolo AE, Bogoch, II, Low N, Cevik M. The role of asymptomatic and pre-symptomatic infection in SARS-CoV-2 transmission-a living systematic review. Clin Microbiol Infect. 2021;27(4):511-9.
58. Byambasuren O, Cardona M, Bell K, Clark J, McLaws M-L, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. medRxiv. 2020:2020.05.10.20097543.
59. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature Medicine. 2020;26(5):672-5.
60. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med. 2020;17(9):e1003346.
61. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. JAMA Intern Med. 2020;180(9):1156-63.
62. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with

coronavirus disease-2019 (COVID-19): duration and key determinants. medRxiv. 2020:2020.06.08.20125310.
63. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9.
64. Kim MC, Cui C, Shin KR, Bae JY, Kweon OJ, Lee MK, et al. Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(7):671-3.
65. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with High Risk for Severe COVID-19: Information for Healthcare Providers 2021 [updated 13.5.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.
66. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. JAMA Network Open. 2020;3(12):e2029058-e.
67. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
68. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLoS One. 2021;16(3):e0247461.
69. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020;383(16):1522-34.
70. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness. Annals of Internal Medicine. 2020;174(3):308-15.
71. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80.e8.
72. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nature Microbiology. 2020;5(4):562-9.
73. Bayati A, Kumar R, Francis V, McPherson PS. SARS-CoV-2 infects cells following viral entry via clathrin-mediated endocytosis. J Biol Chem. 2021;296:100306.
74. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Research. 2008;18(2):290-301.
75. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23.
76. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
77. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature Medicine. 2020;26(5):681-7.
78. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2).

79. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases. 2020;20(5):565-74.
80. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. European Respiratory Journal. 2020;55(4):2000607.
81. Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, et al. The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. J Neuroimmune Pharmacol. 2020;15(3):359-86.
82. Mossel EC, Wang J, Jeffers S, Edeen KE, Wang S, Cosgrove GP, et al. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. Virology. 2008;372(1):127-35.
83. Han S, Mallampalli RK. The Acute Respiratory Distress Syndrome: From Mechanism to Translation. The Journal of Immunology. 2015;194(3):855.
84. Yang C-Y, Chen C-S, Yiang G-T, Cheng Y-L, Yong S-B, Wu M-Y, et al. New Insights into the Immune Molecular Regulation of the Pathogenesis of Acute Respiratory Distress Syndrome. International Journal of Molecular Sciences. 2018;19(2):588.
85. Huang X, Xiu H, Zhang S, Zhang G. The Role of Macrophages in the Pathogenesis of ALI/ARDS. Mediators of Inflammation. 2018;2018:1264913.
86. Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation. Respir Res. 2018;19(1):50.
87. Yip MS, Leung HL, Li PH, Cheung CY, Dutry I, Li D, et al. Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. Hong Kong Med J. 2016;22(3 Suppl 4):25-31.
88. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;395(10235):1517-20.
89. Yang L, Gou J, Gao J, Huang L, Zhu Z, Ji S, et al. Immune characteristics of severe and critical COVID-19 patients. Signal Transduct Target Ther. 2020;5(1):179.
90. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine. 2020;46(5):846-8.
91. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019. Clin Infect Dis. 2020;71(8):1937-42.
92. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clin Infect Dis. 2020;71(16):2027-34.
93. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020;71(15):778-85.
94. Okba NMA, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients. Emerg Infect Dis. 2020;26(7):1478-88.
95. Seow J, Graham C, Merrick B, Acors S, Pickering S, Steel KJA, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat Microbiol. 2020;5(12):1598-607.

96. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371(6529).
97. Crawford KHD, Dingens AS, Eguia R, Wolf CR, Wilcox N, Logue JK, et al. Dynamics of Neutralizing Antibody Titers in the Months After Severe Acute Respiratory Syndrome Coronavirus 2 Infection. J Infect Dis. 2021;223(2):197-205.
98. Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan WH, Chiu SS, et al. Neutralizing antibody titres in SARS-CoV-2 infections. Nat Commun. 2021;12(1):63.
99. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet. 2021;397(10283):1459-69.
100. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet. 2021;397(10280):1204-12.
101. Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, AlMukdad S, et al. Protection against the Omicron Variant from Previous SARS-CoV-2 Infection. The New England journal of medicine. 2022:NEJMc2200133.
102. National Institute of Health. Clinical Spectrum of SARS-CoV-2 Infection 2021 [updated 21.4.21. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/.
103. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-42.
104. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759-65.
105. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-20.
106. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71-7.
107. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? Crit Care. 2020;24(1):198.
108. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama. 2020;323(11):1061-9.
109. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020;38(7):1504-7.
110. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. International Journal of Laboratory Hematology. 2020;42(S1):19-20.
111. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221-30.

112. Berlit P. et al. Neurologische Manifestationen bei COVID-19 – Update vom 22.02.2021 2021 [updated 22.2.21. Available from: https://dgn.org/leitlinien/neurologische-manifestationen-bei-covid-19/.
113. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
114. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
115. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? The Lancet Respiratory Medicine. 2021; [epub ahead of print].
116. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis. 2020; [epub ahead of print].
117. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis. 2020;71(9):2459-68.
118. Devreese KMJ. COVID-19-related laboratory coagulation findings. International journal of laboratory hematology. 2021;43 Suppl 1(Suppl 1):36-42.
119. Len P, Iskakova G, Sautbayeva Z, Kussanova A, Tauekelova AT, Sugralimova MM, et al. Meta-Analysis and Systematic Review of Coagulation Disbalances in COVID-19: 41 Studies and 17,601 Patients. Frontiers in Cardiovascular Medicine. 2022;9.
120. Luo H-C, You C-Y, Lu S-W, Fu Y-Q. Characteristics of coagulation alteration in patients with COVID-19. Ann Hematol. 2021;100(1):45-52.
121. Zhu J, Zhong Z, Ji P, Li H, Li B, Pang J, et al. Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis. Fam Med Community Health. 2020;8(2):e000406.
122. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. New England Journal of Medicine. 2020;382(24):2372-4.
123. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2021, StatPearls Publishing LLC.; 2021.
124. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. Radiology. 2020;296(2):E72-e8.
125. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020;324(8):782-93.
126. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. J Am Coll Radiol. 2020;17(6):701-9.
127. Islam N, Ebrahimzadeh S, Salameh JP, Kazi S, Fabiano N, Treanor L, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database Syst Rev. 2021;3(3):Cd013639.
128. Abrams ER, Rose G, Fields JM, Esener D. Point-of-Care Ultrasound in the Evaluation of COVID-19. J Emerg Med. 2020;59(3):403-8.

129. Peng QY, Wang XT, Zhang LN. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. Intensive Care Med. 2020;46(5):849-50.
130. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database of Systematic Reviews. 2021;2:Cd013665.
131. Caliendo AM, Hanson KE. Covid-19: Diagnosis 2021 [updated 23.6.21. Available from: https://www.uptodate.com/contents/covid-19-diagnosis?search=covid&source=covid19_landing&usage_type=main_section.
132. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases 2020 [updated 19.3.20. Available from: https://www.who.int/publications/i/item/10665-331501.
133. Patel A, Jernigan DB. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak - United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(5):140-6.
134. Centers for Disease Control and Prevention. Interim Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing 2020 [updated 26.2.21. Available from: https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html.
135. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. Jama. 2020;323(18):1843-4.
136. Infectious Diseases Society of America. IDSA Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing 2020 [updated 23.12.20. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/.
137. Yu F, Yan L, Wang N, Yang S, Wang L, Tang Y, et al. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. Clin Infect Dis. 2020;71(15):793-8.
138. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2021;3(3):Cd013705.
139. Infectious Diseases Society of America. IDSA Guidelines on the Diagnosis of COVID-19: Antigen Testing 2021 [updated 27.5.21. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-antigen-testing/.
140. Centers for Disease Control and Prevention. Interim Guidance for Antigen Testing for SARS-CoV-2 2021 [updated 14.6.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html.
141. Lau SK, Woo PC, Wong BH, Tsoi HW, Woo GK, Poon RW, et al. Detection of severe acute respiratory syndrome (SARS) coronavirus nucleocapsid protein in sars patients by enzyme-linked immunosorbent assay. J Clin Microbiol. 2004;42(7):2884-9.
142. Chen Y, Chan KH, Kang Y, Chen H, Luk HK, Poon RW, et al. A sensitive and specific antigen detection assay for Middle East respiratory syndrome coronavirus. Emerg Microbes Infect. 2015;4(4):e26.
143. Mardian Y, Kosasih H, Karyana M, Neal A, Lau CY. Review of Current COVID-19 Diagnostics and Opportunities for Further Development. Front Med (Lausanne). 2021;8:615099.
144. Abbasi J. The Promise and Peril of Antibody Testing for COVID-19. JAMA. 2020;323(19):1881-3.

145. Kontou PI, Braliou GG, Dimou NL, Nikolopoulos G, Bagos PG. Antibody Tests in Detecting SARS-CoV-2 Infection: A Meta-Analysis. Diagnostics (Basel). 2020;10(5):319.
146. US Food and Drug Administration. In Vitro Diagnostics EUAs 2021 [updated 24.5.21. Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas.
147. Infectious Diseases Society of America. IDSA Guidelines on the Diagnosis of COVID-19: Serologic Testing 2020 [updated 18.8.20. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/.
148. Galloway SE PP, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 Lineage — United States, December 29, 2020–January 12, 2021 2021 [updated 15.1.21. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm#suggestedcitation.
149. FIND. Novel variants of SARS-CoV-2 and the impact on diagnostic testing 2021 [updated 11.3.21. Available from: https://www.finddx.org/wp-content/uploads/2021/03/COVID-variants-report-FINAL-12MAR2021.pdf.
150. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; 2021 [Available from: https://www.covid19treatmentguidelines.nih.gov/.
151. Centers for Disease Control and Prevention. What to Do If You Are Sick 2021 [updated 17.3.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html.
152. Centers for Disease Control and Prevention. Isolate If You Are Sick 2021 [updated 18.2.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/isolation.html.
153. Luks AM, Swenson ER. Pulse Oximetry for Monitoring Patients with COVID-19 at Home. Potential Pitfalls and Practical Guidance. Ann Am Thorac Soc. 2020;17(9):1040-6.
154. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of REGEN-COV (casirivimab and imdevimab) 2020 [updated 06.21. Available from: https://www.fda.gov/media/145611/download.
155. Cohen P. COVID-19: Outpatient evaluation and management of acute illness in adults 2022 [updated 25.3.22. Available from: https://www-1uptodate-1com-1wwbz63z60099.han.medunigraz.at/contents/covid-19-outpatient-evaluation-and-management-of-acute-illness-in-adults?search=Coronavirus%20infection&source=search_result&selectedTitle=8~150&usage_type=default&display_rank=6#H915290331.
156. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339.
157. Kim AY, Gandhi RT. COVID-19: Management in hospitalized adults 2021 [updated 12.7.21. Available from: https://www-1uptodate-1com-1wwbz63rf06c1.han.medunigraz.at/contents/covid-19-management-in-hospitalized-adults?search=undefined&source=covid19_landing&usage_type=main_section#H3633193855.
158. Kluge S, et al. S3-Leitlinie - Empfehlungen zur stationären Therapie von Patienten mit COVID-19: AWMF online; 2021 [updated 17.5.21. Available from:

https://www.awmf.org/uploads/tx_szleitlinien/113-001LGl_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19__2021-05.pdf.
159. Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin. S3-Leitlinie Invasive Beatmung und Einsatz extrakorporaler Verfahren bei akuter respiratorischer Insuffizienz: AWMF; 2017 [updated 4.12.17. Available from: https://www.awmf.org/uploads/tx_szleitlinien/001-021l_S3_Invasive_Beatmung_2017-12.pdf.
160. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care. 2020;24(1):597.
161. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care. 2020;10(1):33.
162. Caputo ND, Strayer RJ, Levitan R. Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. Acad Emerg Med. 2020;27(5):375-8.
163. Alhazzani W, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Critical Care Medicine. 2021;49(3):e219-e34.
164. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, et al. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. The Lancet Respiratory Medicine. 2021.
165. World Health Organization. Clinical management of COVID-19: WHO; 2021 [updated 25.1.21. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.
166. AWMF. S3-Leitlinie Prophylaxe der venösen Thromboembolie (VTE): AWMF; 2015 [updated 15.10.15. Available from: https://www.awmf.org/uploads/tx_szleitlinien/003-001l_S3_VTE-Prophylaxe_2015-10-abgelaufen_01.pdf.
167. Patell R, Chiasakul T, Bauer E, Zwicker JI. Pharmacologic Thromboprophylaxis and Thrombosis in Hospitalized Patients with COVID-19: A Pooled Analysis. Thromb Haemost. 2021;121(1):76-85.
168. Brunkhorst FM, Weigand MA, Pletz M, Gastmeier P, Lemmen SW, Meier-Hellmann A, et al. [S3 Guideline Sepsis-prevention, diagnosis, therapy, and aftercare : Long version]. Med Klin Intensivmed Notfmed. 2020;115(Suppl 2):37-109.
169. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020;505:190-1.
170. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-26.
171. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511.
172. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704.

173. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.
174. Zhao M, Zhang J, Li H, Luo Z, Ye J, Xu Y, et al. Recent progress of antiviral therapy for coronavirus disease 2019. Eur J Pharmacol. 2021;890:173646-.
175. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib: FDA; 2020 [updated 19.11.20. Available from: https://www.fda.gov/media/143823/download.
176. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9(12):1407-18.
177. Honein MA, Christie A, Rose DA, Brooks JT, Meaney-Delman D, Cohn A, et al. Summary of Guidance for Public Health Strategies to Address High Levels of Community Transmission of SARS-CoV-2 and Related Deaths, December 2020. MMWR Morb Mortal Wkly Rep. 2020;69(49):1860-7.
178. Centers for Disease Control and Prevention. Ventilation in Buildings 2021 [updated 2.6.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/ventilation.html.
179. Liang M, Gao L, Cheng C, Zhou Q, Uy JP, Heiner K, et al. Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;36:101751.
180. Centers for Disease Control and Prevention. Improve the Fit and Filtration of Your Mask to Reduce the Spread of COVID-19 2021 [updated 6.4.21. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/mask-fit-and-filtration.html.
181. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. JAMA Netw Open. 2020;3(7):e2016818.
182. Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 Test Sensitivity — A Strategy for Containment. New England Journal of Medicine. 2020;383(22):e120.
183. World Health Organization. Mask use in the context of COVID-19 2020 [updated 1.12.20. Available from: https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak.
184. European Medicines Agency. COVID-19 vaccines 2022 [updated —. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines.
185. World Health Organization. Director-General's opening remarks at the media briefing on COVID-19 – 17 May 2021 2020 [updated 17.5.21. Available from: https://www.who.int/director-general/speeches/detail/director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-17-may-2021.
186. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. JAMA Pediatrics. 2021;175(2):143-56.
187. Chu VT, Yousaf AR, Chang K, Schwartz NG, McDaniel CJ, Lee SH, et al. Household Transmission of SARS-CoV-2 from Children and Adolescents. N Engl J Med. 2021;385(10):954-6.

188. Chung E, Chow EJ, Wilcox NC, Burstein R, Brandstetter E, Han PD, et al. Comparison of Symptoms and RNA Levels in Children and Adults With SARS-CoV-2 Infection in the Community Setting. JAMA Pediatr. 2021;175(10):e212025.
189. Goldstein E, Lipsitch M, Cevik M. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. J Infect Dis. 2021;223(3):362-9.
190. Deutsche Gesellschaft für Pädiatrische Infektiologie e.v. Aktualisierte Stellungnahme der Deutschen Gesellschaft für Pädiatrische Infektiologie (DGPI) und der Deutschen Gesellschaft für Krankenhaushygiene (DGKH) zur Rolle von Schulen und Kindertagesstätten in der COVID-19 Pandemie 2021 [updated 18.1.21. Available from: https://dgpi.de/aktualisierte-stellungnahme-der-dgpi-und-der-dgkh-zur-rolle-von-schulen-und-kitas-in-der-covid-19-pandemie-stand-18-01-2021/.
191. Viner RM, Ward JL, Hudson LD, Ashe M, Patel SV, Hargreaves D, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child. 2020.
192. Armann JP, Simon A, Diffloth N, Doenhardt M, Hufnagel M, Trotter A, et al. Hospitalisierungen von Kindern und Jugendlichen mit COVID-19. Dtsch Arztebl International. 2020;117(21):373-4.
193. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-61.
194. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. European Journal of Pediatrics. 2021;180(7):2019-34.
195. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. New England Journal of Medicine. 2020;383(4):334-46.
196. Moritani T, Ekholm S, Westesson P-LA. Diffusion-weighted MR imaging of the brain: Springer Science & Business Media; 2009.
197. Berlit P. The spectrum of vasculopathies in the differential diagnosis of vasculitis. Semin Neurol. 1994;14(4):370-9.
198. Dihlmann S, Peters AS, Hakimi M. [Development of arteriosclerosis]. Pathologe. 2019;40(5):559-72.
199. Böcker W, Denk H, Heitz PU, Moch H, Höfler G, Kreipe H. Pathologie. München: Elsevier Health Sciences; 2012.
200. Fishbein GA, Fishbein MC. Arteriosclerosis: rethinking the current classification. Arch Pathol Lab Med. 2009;133(8):1309-16.
201. Kumar V, Abbas AK, Aster JC. Robbins basic pathology e-book: Elsevier Health Sciences; 2017.
202. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11.
203. Malte L. Facharztwissen Angiologie: zur Vorbereitung auf die Facharztprüfung. Berlin, Heidelberg: Springer; 2019.
204. Hoffman GS, Weyand CM, Langford CA, Goronzy JJ. Inflammatory Diseases of Blood Vessels. 2012.
205. Teng GG, Chatham WW. Vasculitis related to viral and other microbial agents. Best Pract Res Clin Rheumatol. 2015;29(2):226-43.
206. Delaval L, Goulenok T, Achouh P, Saadoun D, Gaudric J, Pellenc Q, et al. New insights on tuberculous aortitis. J Vasc Surg. 2017;66(1):209-15.

207. Polman D, Freilich M, McFarlane IM. Syphilitic Aortitis and Coronary Ostial Stenosis: A Focused Review. American Journal of Medical Case Reports. 2021;9(9):445-50.
208. Töpel I, Zorger N, Steinbauer M. Inflammatory diseases of the aorta: Part 2: Infectious aortitis. Gefasschirurgie. 2016;21(Suppl 2):87-93.
209. Castillo-Martínez D, Amezcua-Guerra LM. Self-reactivity against stress-induced cell molecules: the missing link between Takayasu's arteritis and tuberculosis? Med Hypotheses. 2012;78(4):485-8.
210. Soto ME, Del Carmen Ávila-Casado M, Huesca-Gómez C, Alarcon GV, Castrejon V, Soto V, et al. Detection of IS6110 and HupB gene sequences of Mycobacterium tuberculosis and bovis in the aortic tissue of patients with Takayasu's arteritis. BMC Infect Dis. 2012;12:194.
211. van Timmeren MM, Heeringa P, Kallenberg CG. Infectious triggers for vasculitis. Curr Opin Rheumatol. 2014;26(4):416-23.
212. Javaud N, Certal RDS, Stirnemann J, Morin A-S, Chamouard J-M, Augier A, et al. Tuberculous cerebral vasculitis: Retrospective study of 10 cases. European Journal of Internal Medicine. 2011;22(6):e99-e104.
213. Shukla D, Kalliath J, Dhawan A. Tubercular Retinal Vasculitis: Diagnostic Dilemma and Management Strategies. Clin Ophthalmol. 2021;15:4681-8.
214. Meziane M, Amraoui N, Taoufik H, Mernissi FZ. Cutaneous leukocytoclastic vasculitis revealing multifocal tuberculosis. Int J Mycobacteriol. 2013;2(4):230-2.
215. Ball GV, Fessler BJ, Bridges SL. Oxford textbook of vasculitis. 2014.
216. Lidar M, Lipschitz N, Langevitz P, Shoenfeld Y. The infectious etiology of vasculitis. Autoimmunity. 2009;42(5):432-8.
217. Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. Clin Exp Rheumatol. 2006;24(2 Suppl 41):S71-81.
218. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41(1):95-108.
219. Guillevin L. Infections in vasculitis. Best Pract Res Clin Rheumatol. 2013;27(1):19-31.
220. Rodríguez Bandera AI, Mayor Arenal M, Vorlicka K, Ruiz Bravo-Burguilllos E, Montero Vega D, Vidaurrázaga Díaz-Arcaya C. Acute parvovirus B19 infection in adults: a retrospective study of 49 cases. Actas Dermosifiliogr. 2015;106(1):44-50.
221. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731-40.
222. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrison's principles of internal medicine. New York: McGraw Hill Education; 2018.
223. Merkel PA. Overview of and approach to the vasculitides in adults 2021 [updated 30.3.21. Available from: https://www-1uptodate-1com-1wwbz63uz0002.han.medunigraz.at/contents/overview-of-and-approach-to-the-vasculitides-in-adults?search=vasculitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
224. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nature Reviews Rheumatology. 2022;18(1):22-34.
225. Saadoun D, Vautier M, Cacoub P. Medium- and Large-Vessel Vasculitis. Circulation. 2021;143(3):267-82.
226. Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? Int J Infect Dis. 2005;9(4):185-94.

227. Sundel R. Kawasaki disease: Epidemiology and etiology 2020 [updated 18.5.20. Available from: https://www-1uptodate-1com-1wwbz63e40021.han.medunigraz.at/contents/kawasaki-disease-epidemiology-and-etiology?search=kawasaki%20disease&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4.
228. Jennette JC, Falk RJ. The role of pathology in the diagnosis of systemic vasculitis. Clin Exp Rheumatol. 2007;25(1 Suppl 44):S52-6.
229. Rife E, Gedalia A. Kawasaki Disease: an Update. Current rheumatology reports. 2020;22(10):75-.
230. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020;6(1):71.
231. Scovell S. Superficial vein thrombosis and phlebitis of the lower extremity veins 2022 [updated 18.2.2021. Available from: https://www-1uptodate-1com-1wwbz63gh0068.han.medunigraz.at/contents/superficial-vein-thrombosis-and-phlebitis-of-the-lower-extremity-veins?search=thrombophlebitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
232. Hach-Wunderle V, Gerlach H, Konstantinides S, et al. Interdisziplinäre S2k-Leitlinie: Diagnostik und Therapie der Bein- und Beckenvenenthrombose und der Lungenembolie: AWMF; 2016 [updated 10.10.2015. Available from: https://www.awmf.org/uploads/tx_szleitlinien/065-002l_S2k_VTE_2016-01.pdf.
233. Leon L, Giannoukas AD, Dodd D, Chan P, Labropoulos N. Clinical significance of superficial vein thrombosis. Eur J Vasc Endovasc Surg. 2005;29(1):10-7.
234. Meissner MH, Wakefield TW, Ascher E, Caprini JA, Comerota AJ, Eklof B, et al. Acute venous disease: venous thrombosis and venous trauma. J Vasc Surg. 2007;46 Suppl S:25s-53s.
235. De Maeseneer MG. Superficial thrombophlebitis of the lower limb: practical recommendations for diagnosis and treatment. Acta Chir Belg. 2005;105(2):145-7.
236. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016;388(10063):3060-73.
237. Giordano NJ, Jansson PS, Young MN, Hagan KA, Kabrhel C. Epidemiology, Pathophysiology, Stratification, and Natural History of Pulmonary Embolism. Tech Vasc Interv Radiol. 2017;20(3):135-40.
238. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69, 69a-69k.
239. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9.
240. Pöss J, Freund A, Vollert JO, Wolfrum S, Radke P, Möckel M, et al. Lungenarterienembolie. Der Kardiologe. 2018;12(1):68-82.
241. Zuurbier SM, Coutinho JM. Cerebral Venous Thrombosis. Adv Exp Med Biol. 2017;906:183-93.
242. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. Stroke. 2012;43(12):3375-7.
243. Janghorbani M, Zare M, Saadatnia M, Mousavi SA, Mojarrad M, Asgari E. Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: frequency and seasonal variation. Acta Neurol Scand. 2008;117(2):117-21.

244. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F. Cerebral vein and dural sinus thrombosis in elderly patients. Stroke. 2005;36(9):1927-32.
245. Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Cantú C, Bousser MG, et al. Cerebral venous and sinus thrombosis in women. Stroke. 2009;40(7):2356-61.
246. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med. 1998;338(25):1793-7.
247. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664-70.
248. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791-8.
249. Duman T, Uluduz D, Midi I, Bektas H, Kablan Y, Goksel BK, et al. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. Journal of Stroke and Cerebrovascular Diseases. 2017;26(8):1848-57.
250. Pfefferkorn T, Crassard I, Linn J, Dichgans M, Boukobza M, Bousser MG. Clinical features, course and outcome in deep cerebral venous system thrombosis: an analysis of 32 cases. J Neurol. 2009;256(11):1839-45.
251. von Mering M, Stiefel M, Brockmann K, Nau R. Deep cerebral venous sinus thrombosis often presents with neuropsychologic symptoms. J Clin Neurosci. 2003;10(3):310-2.
252. Coutinho JM, van den Berg R, Zuurbier SM, VanBavel E, Troost D, Majoie CB, et al. Small juxtacortical hemorrhages in cerebral venous thrombosis. Ann Neurol. 2014;75(6):908-16.
253. Saposnik G, Barinagarrementeria F, Brown RD, Jr., Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158-92.
254. Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2012;10(4):582-9.
255. Ferro JM, Aguiar de Sousa D. Cerebral Venous Thrombosis: an Update. Curr Neurol Neurosci Rep. 2019;19(10):74.
256. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. Circulation. 2022;145(8):e153-e639.
257. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364-e467.
258. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal. 2019;41(1):111-88.
259. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):e618-e51.
260. Anderson JL, Morrow DA. Acute Myocardial Infarction. N Engl J Med. 2017;376(21):2053-64.

261. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
262. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med. 2014;371(9):818-27.
263. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004-13.
264. Libby P, Bornfeldt KE, Tall AR. Atherosclerosis: Successes, Surprises, and Future Challenges. Circ Res. 2016;118(4):531-4.
265. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. Eur Heart J. 2015;36(8):475-81.
266. Wanamaker BL, Seth MM, Sukul D, Dixon SR, Bhatt DL, Madder RD, et al. Relationship Between Troponin on Presentation and In‐Hospital Mortality in Patients With ST‐Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Journal of the American Heart Association. 2019;8(19):e013551.
267. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2020;42(14):1289-367.
268. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2017;39(2):119-77.
269. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145-53.
270. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.
271. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.
272. Silvain J, Beygui F, Barthélémy O, Pollack C, Jr., Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. Bmj. 2012;344:e553.
273. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet. 2000;355(9219):1936-42.
274. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J. 2006;27(7):779-88.

275. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124(23):2512-21.
276. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013;368(15):1379-87.
277. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J. 2010;31(17):2156-69.
278. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. Eur Heart J. 2011;32(8):972-82.
279. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77.
280. Björck M, Earnshaw JJ, Acosta S, Bastos Gonçalves F, Cochennec F, Debus ES, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia. Eur J Vasc Endovasc Surg. 2020;59(2):173-218.
281. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5-67.
282. Olinic D-M, Stanek A, Tătaru D-A, Homorodean C, Olinic M. Acute Limb Ischemia: An Update on Diagnosis and Management. J Clin Med. 2019;8(8):1215.
283. Lawall H, Huppert P, Rümenapf G, Diehm C. Periphere arterielle Verschlusskrankheit (PAVK)–S3-Leitlinie Diagnostik und Therapie. Der Klinikarzt. 2011;40(11):502-10.
284. Simon F, Busch A, Oberhuber A, Schelzig H, Duran M. Pathophysiologie der akuten Extremitätenischämie. Gefässchirurgie. 2016;21(2):91-5.
285. Mai V, Tan BK, Mainbourg S, Potus F, Cucherat M, Lega JC, et al. Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: A systematic review with meta-analysis. Vascul Pharmacol. 2021;139:106882.
286. Tufano A, Rendina D, Abate V, Casoria A, Marra A, Buonanno P, et al. Venous Thromboembolism in COVID-19 Compared to Non-COVID-19 Cohorts: A Systematic Review with Meta-Analysis. J Clin Med. 2021;10(21):4925.
287. Pothineni NVK, Subramany S, Kuriakose K, Shirazi LF, Romeo F, Shah PK, et al. Infections, atherosclerosis, and coronary heart disease. Eur Heart J. 2017;38(43):3195-201.
288. Giryes S, Bragazzi NL, Bridgewood C, De Marco G, McGonagle D. COVID-19 Vasculitis and vasculopathy-Distinct immunopathology emerging from the close juxtaposition of Type II Pneumocytes and Pulmonary Endothelial Cells. Semin Immunopathol. 2022;44(3):375-90.
289. McGonagle D, Bridgewood C, Ramanan AV, Meaney JFM, Watad A. COVID-19 vasculitis and novel vasculitis mimics. Lancet Rheumatol. 2021;3(3):e224-e33.
290. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8.

291. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003;23(2):168-75.
292. Dittmayer C, Meinhardt J, Radbruch H, Radke J, Heppner BI, Heppner FL, et al. Why misinterpretation of electron micrographs in SARS-CoV-2-infected tissue goes viral. Lancet. 2020;396(10260):e64-e5.
293. Goldsmith CS, Miller SE, Martines RB, Bullock HA, Zaki SR. Electron microscopy of SARS-CoV-2: a challenging task. Lancet. 2020;395(10238):e99.
294. Nicosia RF, Ligresti G, Caporarello N, Akilesh S, Ribatti D. COVID-19 Vasculopathy: Mounting Evidence for an Indirect Mechanism of Endothelial Injury. Am J Pathol. 2021;191(8):1374-84.
295. McCracken IR, Saginc G, He L, Huseynov A, Daniels A, Fletcher S, et al. Lack of Evidence of Angiotensin-Converting Enzyme 2 Expression and Replicative Infection by SARS-CoV-2 in Human Endothelial Cells. Circulation. 2021;143(8):865-8.
296. Schimmel L, Chew KY, Stocks CJ, Yordanov TE, Essebier P, Kulasinghe A, et al. Endothelial cells are not productively infected by SARS-CoV-2. Clin Transl Immunology. 2021;10(10):e1350.
297. Thacker VV, Sharma K, Dhar N, Mancini G-F, Sordet-Dessimoz J, McKinney JD. Rapid endotheliitis and vascular damage characterize SARS-CoV-2 infection in a human lung-on-chip model. EMBO Rep. 2021;22(6):e52744-e.
298. Satturwar S, Fowkes M, Farver C, Wilson AM, Eccher A, Girolami I, et al. Postmortem Findings Associated With SARS-CoV-2: Systematic Review and Meta-analysis. Am J Surg Pathol. 2021;45(5):587-603.
299. Magro CM, Mulvey J, Kubiak J, Mikhail S, Suster D, Crowson AN, et al. Severe COVID-19: A multifaceted viral vasculopathy syndrome. Ann Diagn Pathol. 2021;50:151645.
300. Birnhuber A, Fließer E, Gorkiewicz G, Zacharias M, Seeliger B, David S, et al. Between inflammation and thrombosis: endothelial cells in COVID-19. European Respiratory Journal. 2021;58(3):2100377.
301. O'Sullivan JM, Gonagle DM, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. Lancet Haematol. 2020;7(8):e553-e5.
302. Frantzeskaki F, Armaganidis A, Orfanos SE. Immunothrombosis in Acute Respiratory Distress Syndrome: Cross Talks between Inflammation and Coagulation. Respiration. 2017;93(3):212-25.
303. Milsom C, Rak J. Tissue factor and cancer. Pathophysiol Haemost Thromb. 2008;36(3-4):160-76.
304. Asokananthan N, Graham PT, Fink J, Knight DA, Bakker AJ, McWilliam AS, et al. Activation of protease-activated receptor (PAR)-1, PAR-2, and PAR-4 stimulates IL-6, IL-8, and prostaglandin E2 release from human respiratory epithelial cells. J Immunol. 2002;168(7):3577-85.
305. Ruf W. New players in the sepsis-protective activated protein C pathway. J Clin Invest. 2010;120(9):3084-7.
306. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nature Reviews Immunology. 2013;13(1):34-45.
307. Tanguay JF, Geoffroy P, Sirois MG, Libersan D, Kumar A, Schaub RG, et al. Prevention of in-stent restenosis via reduction of thrombo-inflammatory reactions with recombinant P-selectin glycoprotein ligand-1. Thromb Haemost. 2004;91(6):1186-93.
308. Martinod K, Deppermann C. Immunothrombosis and thromboinflammation in host defense and disease. Platelets. 2021;32(3):314-24.

309. Bonaventura A, Vecchié A, Dagna L, Martinod K, Dixon DL, Van Tassell BW, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. Nat Rev Immunol. 2021;21(5):319-29.
310. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133(9):906-18.
311. Cenko E, Badimon L, Bugiardini R, Claeys MJ, De Luca G, de Wit C, et al. Cardiovascular disease and COVID-19: a consensus paper from the ESC Working Group on Coronary Pathophysiology & Microcirculation, ESC Working Group on Thrombosis and the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Heart Rhythm Association (EHRA). Cardiovasc Res. 2021;117(14):2705-29.
312. Goswami J, MacArthur TA, Sridharan M, Pruthi RK, McBane RD, 2nd, Witzig TE, et al. A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. Shock. 2021;55(6):700-16.
313. Levi M, van der Poll T. Coagulation and sepsis. Thrombosis Research. 2017;149:38-44.
314. Subramaniam S, Scharrer I. Procoagulant activity during viral infections. Front Biosci (Landmark Ed). 2018;23(6):1060-81.
315. Kreutz R, Algharably EAE-H, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovascular research. 2020;116(10):1688-99.
316. Murray E, Tomaszewski M, Guzik TJ. Binding of SARS-CoV-2 and angiotensin-converting enzyme 2: clinical implications. Cardiovascular research. 2020;116(7):e87-e9.
317. Pucci F, Annoni F, Dos Santos RAS, Taccone FS, Rooman M. Quantifying Renin-Angiotensin-System Alterations in COVID-19. Cells. 2021;10(10):2755.
318. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, et al. Immunothrombotic Dysregulation in COVID-19 Pneumonia Is Associated With Respiratory Failure and Coagulopathy. Circulation. 2020;142(12):1176-89.
319. Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. The Lancet Haematology. 2020;7(8):e575-e82.
320. Juneja GK, Castelo M, Yeh CH, Cerroni SE, Hansen BE, Chessum JE, et al. Biomarkers of coagulation, endothelial function, and fibrinolysis in critically ill patients with COVID-19: A single-center prospective longitudinal study. Journal of thrombosis and haemostasis : JTH. 2021;19(6):1546-57.
321. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020;195:219-25.
322. Hamzeh-Cognasse H, Mansour A, Reizine F, Mismetti P, Gouin-Thibault I, Cognasse F. Platelet-derived sCD40L: specific inflammatory marker for early-stage severe acute respiratory syndrome coronavirus 2 infection. Virology Journal. 2021;18(1):211.
323. Chioh FW, Fong S-W, Young BE, Wu K-X, Siau A, Krishnan S, et al. Convalescent COVID-19 patients are susceptible to endothelial dysfunction due to persistent immune activation. Elife. 2021;10:e64909.
324. Fogarty H, Townsend L, Morrin H, Ahmad A, Comerford C, Karampini E, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. J Thromb Haemost. 2021;19(10):2546-53.

325. Jud P, Gressenberger P, Muster V, Avian A, Meinitzer A, Strohmaier H, et al. Evaluation of Endothelial Dysfunction and Inflammatory Vasculopathy After SARS-CoV-2 Infection-A Cross-Sectional Study. Front Cardiovasc Med. 2021;8:750887.
326. Andrianto, Al-Farabi MJ, Nugraha RA, Marsudi BA, Azmi Y. Biomarkers of endothelial dysfunction and outcomes in coronavirus disease 2019 (COVID-19) patients: A systematic review and meta-analysis. Microvasc Res. 2021;138:104224.
327. Doevelaar AAN, Bachmann M, Hölzer B, Seibert FS, Rohn BJ, Bauer F, et al. von Willebrand Factor Multimer Formation Contributes to Immunothrombosis in Coronavirus Disease 2019. Crit Care Med. 2021;49(5):e512-e20.
328. Sinkovits G, Réti M, Müller V, Iványi Z, Gál J, Gopcsa L, et al. Associations between the von Willebrand Factor-ADAMTS13 Axis, Complement Activation, and COVID-19 Severity and Mortality. Thromb Haemost. 2022;122(2):240-56.
329. Lipcsey M, Persson B, Eriksson O, Blom AM, Fromell K, Hultström M, et al. The Outcome of Critically Ill COVID-19 Patients Is Linked to Thromboinflammation Dominated by the Kallikrein/Kinin System. Front Immunol. 2021;12:627579.
330. Cabrera LE, Pekkarinen PT, Alander M, Nowlan KHA, Nguyen NA, Jokiranta S, et al. Characterization of low-density granulocytes in COVID-19. PLoS pathogens. 2021;17(7):e1009721-e.
331. Denny MF, Yalavarthi S, Zhao W, Thacker SG, Anderson M, Sandy AR, et al. A distinct subset of proinflammatory neutrophils isolated from patients with systemic lupus erythematosus induces vascular damage and synthesizes type I IFNs. J Immunol. 2010;184(6):3284-97.
332. Leppkes M, Knopf J, Naschberger E, Lindemann A, Singh J, Herrmann I, et al. Vascular occlusion by neutrophil extracellular traps in COVID-19. EBioMedicine. 2020;58:102925-.
333. Veras FP, Pontelli MC, Silva CM, Toller-Kawahisa JE, de Lima M, Nascimento DC, et al. SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology. J Exp Med. 2020;217(12).
334. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. 2020;5(11).
335. Englert H, Rangaswamy C, Deppermann C, Sperhake JP, Krisp C, Schreier D, et al. Defective NET clearance contributes to sustained FXII activation in COVID-19-associated pulmonary thrombo-inflammation. EBioMedicine. 2021;67:103382.
336. Middleton EA, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood. 2020;136(10):1169-79.
337. Ng H, Havervall S, Rosell A, Aguilera K, Parv K, Meijenfeldt FAv, et al. Circulating Markers of Neutrophil Extracellular Traps Are of Prognostic Value in Patients With COVID-19. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021;41(2):988-94.
338. Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest. 2020;130(11):6151-7.
339. Manfredi AA, Rovere-Querini P, D'Angelo A, Maugeri N. Low molecular weight heparins prevent the induction of autophagy of activated neutrophils and the formation of neutrophil extracellular traps. Pharmacol Res. 2017;123:146-56.
340. Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. Thorax. 2021;76(10):970-9.

341. Zhang R, Ni L, Di X, Wang X, Ma B, Niu S, et al. Systematic review and meta-analysis of the prevalence of venous thromboembolic events in novel coronavirus disease-2019 patients. J Vasc Surg Venous Lymphat Disord. 2021;9(2):289-98.e5.
342. Roberts LN, Navaratnam AV, Arya R, Briggs TWR, Gray WK. Venous thromboembolism in patients hospitalised with COVID-19 in England. Thromb Res. 2022;213:138-44.
343. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. Vasc Med. 2021;26(4):415-25.
344. Huisman MV, Barco S, Cannegieter SC, Le Gal G, Konstantinides SV, Reitsma PH, et al. Pulmonary embolism. Nat Rev Dis Primers. 2018;4:18028.
345. Girard P, Sanchez O, Leroyer C, Musset D, Meyer G, Stern JB, et al. Deep venous thrombosis in patients with acute pulmonary embolism: prevalence, risk factors, and clinical significance. Chest. 2005;128(3):1593-600.
346. Gómez CA, Sun CK, Tsai IT, Chang YP, Lin MC, Hung IY, et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. Sci Rep. 2021;11(1):16025.
347. Candeloro M, Schulman S. Arterial Thrombotic Events in Hospitalized COVID-19 Patients: A Short Review and Meta-Analysis. Semin Thromb Hemost. 2022.
348. Glober N, Stewart L, Seo J, Kabrhel C, Nordenholz K, Camargo C, et al. Incidence and characteristics of arterial thromboemboli in patients with COVID-19. Thrombosis Journal. 2021;19(1):104.
349. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. Jama. 2020;324(8):799-801.
350. Jenner WJ, Kanji R, Mirsadraee S, Gue YX, Price S, Prasad S, et al. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. Journal of thrombosis and thrombolysis. 2021;51(3):595-607.
351. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. JAMA Netw Open. 2021;4(6):e2116420.
352. Karagiannidis C, Sander LE, Mall MA, Busse R. Incidence and outcomes of SARS-CoV-2-associated PIMS in Germany: a nationwide analysis. Infection. 2022:1-3.
353. Li JY, Wang HF, Yin P, Li D, Wang DL, Peng P, et al. Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicenter retrospective study. J Thromb Haemost. 2021;19(4):1038-48.
354. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98.
355. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation. 2020;142(2):184-6.
356. Thomas MR, Scully M. Clinical features of thrombosis and bleeding in COVID-19. Blood. 2022;140(3):184-95.
357. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149.

358. Fernández-Capitán C, Barba R, Díaz-Pedroche MDC, Sigüenza P, Demelo-Rodriguez P, Siniscalchi C, et al. Presenting Characteristics, Treatment Patterns, and Outcomes among Patients with Venous Thromboembolism during Hospitalization for COVID-19. Semin Thromb Hemost. 2021;47(4):351-61.
359. Jiménez S, Miró Ò, Llorens P, Martín-Sánchez FJ, Burillo-Putze G, Piñera P, et al. Incidence, risk factors, clinical characteristics and outcomes of deep venous thrombosis in patients with COVID-19 attending the Emergency Department: results of the UMC-19-S8. Eur J Emerg Med. 2021;28(3):218-26.
360. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020;75(23):2950-73.
361. García-Sanz MT, Pena-Álvarez C, López-Landeiro P, Bermo-Domínguez A, Fontúrbel T, González-Barcala FJ. Symptoms, location and prognosis of pulmonary embolism. Revista Portuguesa de Pneumologia. 2014;20(4):194-9.
362. Gąsecka A, Borovac JA, Guerreiro RA, Giustozzi M, Parker W, Caldeira D, et al. Thrombotic Complications in Patients with COVID-19: Pathophysiological Mechanisms, Diagnosis, and Treatment. Cardiovascular Drugs and Therapy. 2021;35(2):215-29.
363. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14.
364. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China. Circulation. 2020;142(2):114-28.
365. Amboss. Phlebothrombose (Tiefe Beinvenenthrombose) 2022 [updated 22.07.2022. Available from: https://next.amboss.com/de/article/fh0kWf.
366. Liu Y, Cai J, Wang C, Jin J, Qu L. A systematic review and meta-analysis of incidence, prognosis, and laboratory indicators of venous thromboembolism in hospitalized patients with coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(5):1099-111.e6.
367. Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. Thromb Res. 2020;195:95-9.
368. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. Chest. 2020;158(3):1143-63.
369. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1859-65.
370. Marini CP, Lewis E, Petrone P, Zenilman A, Lu Z, Rivera A, et al. Incidence and effects of deep vein thrombosis on the outcome of patients with coronavirus disease 2019 infection. J Vasc Surg Venous Lymphat Disord. 2022;10(4):803-10.
371. Chang H, Rockman CB, Jacobowitz GR, Speranza G, Johnson WS, Horowitz JM, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(3):597-604.
372. Spirk D, Husmann M, Hayoz D, Baldi T, Frauchiger B, Engelberger R, et al. Predictors of in-hospital mortality in elderly patients with acute venous thrombo-embolism: the SWIss Venous ThromboEmbolism Registry (SWIVTER). European Heart Journal. 2011;33(7):921-6.

373. Miró Ò, Jiménez S, Llorens P, Roussel M, Gorlicki J, García-Lamberechts EJ, et al. Pulmonary embolism severity and in-hospital mortality: An international comparative study between COVID-19 and non-COVID patients. Eur J Intern Med. 2022;98:69-76.
374. Baldini T, Asioli GM, Romoli M, Carvalho Dias M, Schulte EC, Hauer L, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: A systematic review and meta-analysis. Eur J Neurol. 2021;28(10):3478-90.
375. Bousser M-G, Ferro JM. Cerebral venous thrombosis: an update. The Lancet Neurology. 2007;6(2):162-70.
376. Al-Mufti F, Amuluru K, Sahni R, Bekelis K, Karimi R, Ogulnick J, et al. Cerebral Venous Thrombosis in COVID-19: A New York Metropolitan Cohort Study. AJNR Am J Neuroradiol. 2021;42(7):1196-200.
377. Abdalkader M, Shaikh SP, Siegler JE, Cervantes-Arslanian AM, Tiu C, Radu RA, et al. Cerebral Venous Sinus Thrombosis in COVID-19 Patients: A Multicenter Study and Review of Literature. J Stroke Cerebrovasc Dis. 2021;30(6):105733.
378. Ghosh R, Roy D, Mandal A, Pal SK, Chandra Swaika B, Naga D, et al. Cerebral venous thrombosis in COVID-19. Diabetes Metab Syndr. 2021;15(3):1039-45.
379. Ostovan VR, Foroughi R, Rostami M, Almasi-Dooghaee M, Esmaili M, Bidaki AA, et al. Cerebral venous sinus thrombosis associated with COVID-19: a case series and literature review. J Neurol. 2021;268(10):3549-60.
380. Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. J Neurol. 2022;269(4):1731-40.
381. Vogrig A, Gigli GL, Bnà C, Morassi M. Stroke in patients with COVID-19: Clinical and neuroimaging characteristics. Neurosci Lett. 2021;743:135564.
382. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. Stroke. 2020;51(7):2002-11.
383. Azzimondi G, Nonino F, Fiorani L, Vignatelli L, Stracciari A, Pazzaglia P, et al. Incidence of stroke among inpatients in a large Italian hospital. Stroke. 1994;25(9):1752-4.
384. Cumbler E. In-Hospital Ischemic Stroke. Neurohospitalist. 2015;5(3):173-81.
385. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of Ischemic Stroke in Patients with Covid-19 versus Patients with Influenza. medRxiv. 2020.
386. Park HJ, Cho HJ, Kim YD, Lee DW, Choi HY, Kim SM, et al. Comparison of the characteristics for in-hospital and out-of-hospital ischaemic strokes. Eur J Neurol. 2009;16(5):582-8.
387. Syahrul S, Maliga HA, Ilmawan M, Fahriani M, Mamada SS, Fajar JK, et al. Hemorrhagic and ischemic stroke in patients with coronavirus disease 2019: incidence, risk factors, and pathogenesis - a systematic review and meta-analysis. F1000Res. 2021;10:34.
388. Arboix A, Blanco-Rojas L, Martí-Vilalta JL. Advancements in understanding the mechanisms of symptomatic lacunar ischemic stroke: translation of knowledge to prevention strategies. Expert Rev Neurother. 2014;14(3):261-76.
389. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke. Circulation Research. 2017;120(3):527-40.
390. Saber H, Saver JL. Distributional Validity and Prognostic Power of the National Institutes of Health Stroke Scale in US Administrative Claims Data. JAMA Neurology. 2020;77(5):606-12.
391. Shahjouei S, Tsivgoulis G, Farahmand G, Koza E, Mowla A, Sadr AV, et al. SARS-CoV-2 and Stroke Characteristics. Stroke. 2021;52(5):e117-e30.

392. Yew KS, Cheng E. Acute stroke diagnosis. Am Fam Physician. 2009;80(1):33-40.
393. Ghasemi M, Umeton RP, Keyhanian K, Mohit B, Rahimian N, Eshaghhosseiny N, et al. SARS-CoV-2 and Acute Cerebrovascular Events: An Overview. J Clin Med. 2021;10(15).
394. Strambo D, De Marchis GM, Bonati LH, Arnold M, Carrera E, Galletta S, et al. Ischemic stroke in COVID-19 patients: Mechanisms, treatment, and outcomes in a consecutive Swiss Stroke Registry analysis. Eur J Neurol. 2022;29(3):732-43.
395. Cucchiara B. COVID-19: Neurologic complications and management of neurologic conditions 2022 [updated 7.4.2022. Available from: https://www.uptodate.com/contents/covid-19-neurologic-complications-and-management-of-neurologic-conditions?search=Covid%2019%20AND%20stroke&source=covid19_landing&usage_type=main_section#H125054315.
396. Qureshi AI, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: Insights from an international panel. Am J Emerg Med. 2020;38(7):1548.e5-.e7.
397. Ospel JM, Goyal M. Endovascular stroke treatment during the COVID-19 pandemic. Nat Rev Neurol. 2020;16(7):351-2.
398. Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, et al. Acute Ischemic Stroke and COVID-19. Stroke. 2021;52(3):905-12.
399. Jiang J, Tan C, Zhou W, Peng W, Zhou X, Du J, et al. Plasma C-Reactive Protein Level and Outcome of Acute Ischemic Stroke Patients Treated by Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. European Neurology. 2021;84(3):145-50.
400. Simonetto M, Wechsler PM, Merkler AE. Stroke Treatment in the Era of COVID-19: a Review. Curr Treat Options Neurol. 2022;24(4):155-71.
401. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol. 2012;56(1):129-36.
402. Al-Smadi AS, Mach JC, Abrol S, Luqman A, Chamiraju P, Abujudeh H. Endovascular Thrombectomy of COVID-19-Related Large Vessel Occlusion: A Systematic Review and Summary of the Literature. Current Radiology Reports. 2021;9(4):4.
403. Cappellari M, Zini A, Sangalli D, Cavallini A, Reggiani M, Sepe FN, et al. Thrombolysis and bridging therapy in patients with acute ischaemic stroke and Covid-19. European Journal of Neurology. 2020;27(12):2641-5.
404. Katz JM, Libman RB, Wang JJ, Sanelli P, Filippi CG, Gribko M, et al. Cerebrovascular Complications of COVID-19. Stroke. 2020;51(9):e227-e31.
405. Akhtar N, Abid F, Singh R, Kamran S, Imam Y, Al Jerdi S, et al. Characteristics and comparisons of acute stroke in "recovered" to "active COVID-19 and "pre-pandemic" in Qatar database. J Thromb Thrombolysis. 2022;53(4):824-8.
406. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain. 2020;143(10):3089-103.
407. Sennfält S, Norrving B, Petersson J, Ullberg T. Long-Term Survival and Function After Stroke. Stroke. 2019;50(1):53-61.
408. Ward A, Sarraju A, Lee D, Bhasin K, Gad S, Beetel R, et al. COVID-19 is associated with higher risk of venous thrombosis, but not arterial thrombosis,

compared with influenza: Insights from a large US cohort. PLoS One. 2022;17(1):e0261786.
409. Chaudhary R, Padrnos L, Wysokinska E, Pruthi R, Misra S, Sridharan M, et al. Macrovascular Thrombotic Events in a Mayo Clinic Enterprise-Wide Sample of Hospitalized COVID-19-Positive Compared With COVID-19-Negative Patients. Mayo Clin Proc. 2021;96(7):1718-26.
410. Milovančev A, Petrović M, Popadić V, Miljković T, Klašnja S, Djuran P, et al. Characteristics and Outcomes of Patients with Acute Coronary Syndrome and COVID-19. J Clin Med. 2022;11(7).
411. Garcia S, Dehghani P, Grines C, Davidson L, Nayak KR, Saw J, et al. Initial Findings From the North American COVID-19 Myocardial Infarction Registry. Journal of the American College of Cardiology. 2021;77(16):1994-2003.
412. Gitto M, Novelli L, Reimers B, Condorelli G, Stefanini G. Specific characteristics of STEMI in COVID-19 patients and their practical implications. Kardiologia Polska (Polish Heart Journal). 2022;80(3):266-77.
413. Kumar N, Verma R, Lohana P, Lohana A, Ramphul K. Acute myocardial infarction in COVID-19 patients. A review of cases in the literature. Arch Med Sci Atheroscler Dis. 2021;6:e169-e75.
414. De Luca G, Verdoia M, Cercek M, Jensen LO, Vavlukis M, Calmac L, et al. Impact of COVID-19 Pandemic on Mechanical Reperfusion for Patients With STEMI. Journal of the American College of Cardiology. 2020;76(20):2321-30.
415. Ghasemzadeh N, Kim N, Amlani S, Madan M, Shavadia JS, Chong AY, et al. A Review of ST-Elevation Myocardial Infarction in Patients with COVID-19. Cardiol Clin. 2022;40(3):321-8.
416. Popovic B, Varlot J, Metzdorf PA, Jeulin H, Goehringer F, Camenzind E. Changes in characteristics and management among patients with ST-elevation myocardial infarction due to COVID-19 infection. Catheter Cardiovasc Interv. 2021;97(3):E319-e26.
417. Rodriguez-Leor O, Cid Alvarez AB, Pérez de Prado A, Rossello X, Ojeda S, Serrador A, et al. In-hospital outcomes of COVID-19 ST-elevation myocardial infarction patients. EuroIntervention. 2021;16(17):1426-33.
418. Garcia S, Dehghani P, Stanberry L, Grines C, Patel RAG, Nayak KR, et al. Trends in Clinical Presentation, Management, and Outcomes of STEMI in Patients With COVID-19. J Am Coll Cardiol. 2022;79(22):2236-44.
419. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, et al. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2020;76(10):1168-76.
420. Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, et al. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis. Cardiovasc Res. 2022;118(6):1385-412.
421. Mahmud E, Dauerman HL, Welt FGP, Messenger JC, Rao SV, Grines C, et al. Management of acute myocardial infarction during the COVID-19 pandemic: A Consensus Statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). Catheter Cardiovasc Interv. 2020;96(2):336-45.
422. Cardiology TTFftmoC-otESo. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up. Cardiovascular Research. 2021;118(7):1618-66.

423. Chew NWS, Ow ZGW, Teo VXY, Heng RRY, Ng CH, Lee C-H, et al. The Global Effect of the COVID-19 Pandemic on STEMI Care: A Systematic Review and Meta-analysis. Canadian Journal of Cardiology. 2021;37(9):1450-9.
424. Topcu AC, Ozturk-Altunyurt G, Akman D, Batirel A, Demirhan R. Acute Limb Ischemia in Hospitalized COVID-19 Patients. Ann Vasc Surg. 2021;74:88-94.
425. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events: Implications for Prevention. Circulation. 2015;132(19):1805-15.
426. Wohlauer MVea. COVID-19: Acute limb ischemia 2021 [updated 16.08.2021. Available from: https://www.uptodate.com/contents/covid-19-acute-limb-ischemia?search=Covid%2019%20acute%20limb%20ischemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1685778155.
427. Attisani L, Pucci A, Luoni G, Luzzani L, Pegorer MA, Settembrini AM, et al. COVID-19 and acute limb ischemia: a systematic review. J Cardiovasc Surg (Torino). 2021;62(6):542-7.
428. Bellosta R, Luzzani L, Natalini G, Pegorer MA, Attisani L, Cossu LG, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg. 2020;72(6):1864-72.
429. Ilonzo N, Judelson D, Al-Jundi W, Etkin Y, O'Banion LA, Rivera A, et al. A review of acute limb ischemia in COVID-positive patients. Semin Vasc Surg. 2021;34(2):8-12.
430. Ilonzo N, Rao A, Safir S, Vouyouka A, Phair J, Baldwin M, et al. Acute thrombotic manifestations of coronavirus disease 2019 infection: Experience at a large New York City health care system. Journal of Vascular Surgery. 2021;73(3):789-96.
431. Goldman IA, Ye K, Scheinfeld MH. Lower-extremity Arterial Thrombosis Associated with COVID-19 Is Characterized by Greater Thrombus Burden and Increased Rate of Amputation and Death. Radiology. 2020;297(2):E263-e9.
432. Sánchez JB, Cuipal Alcalde JD, Ramos Isidro R, Luna CZ, Cubas WS, Coaguila Charres A, et al. Acute Limb Ischemia in a Peruvian Cohort Infected by COVID-19. Annals of Vascular Surgery. 2021;72:196-204.
433. Hemingway J, Emanuels D, Aarabi S, Quiroga E, Tran N, Starnes B, et al. Safety of transfer, type of procedure, and factors predictive of limb salvage in a modern series of acute limb ischemia. Journal of Vascular Surgery. 2019;69(4):1174-9.
434. Kempe K, Starr B, Stafford JM, Islam A, Mooney A, Lagergren E, et al. Results of surgical management of acute thromboembolic lower extremity ischemia. Journal of Vascular Surgery. 2014;60(3):702-7.
435. Jongkind V, Earnshaw JJ, Bastos Gonçalves F, Cochennec F, Debus ES, Hinchliffe R, et al. Editor's Choice - Update of the European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Acute Limb Ischaemia in Light of the COVID-19 Pandemic, Based on a Scoping Review of the Literature. Eur J Vasc Endovasc Surg. 2022;63(1):80-9.
436. Fournier M, Faille D, Dossier A, Mageau A, Nicaise Roland P, Ajzenberg N, et al. Arterial Thrombotic Events in Adult Inpatients With COVID-19. Mayo Clinic Proceedings. 2021;96(2):295-303.
437. Parisi R, Costanzo S, Di Castelnuovo A, de Gaetano G, Donati MB, Iacoviello L. Different Anticoagulant Regimens, Mortality, and Bleeding in Hospitalized Patients with COVID-19: A Systematic Review and an Updated Meta-Analysis. Semin Thromb Hemost. 2021;47(4):372-91.

438. Galyfos G, Sianou A, Frountzas M, Vasilios K, Vouros D, Theodoropoulos C, et al. Acute limb ischemia among patients with COVID-19 infection. J Vasc Surg. 2022;75(1):326-42.
439. Etkin Y, Conway AM, Silpe J, Qato K, Carroccio A, Manvar-Singh P, et al. Acute Arterial Thromboembolism in Patients with COVID-19 in the New York City Area. Annals of Vascular Surgery. 2021;70:290-4.
440. Gonzalez-Fajardo JA, Ansuategui M, Romero C, Comanges A, Gómez-Arbeláez D, Ibarra G, et al. Mortalidad de los pacientes covid-19 con complicaciones trombóticas. Medicina Clínica. 2021;156(3):112-7.
441. Kahlberg A, Mascia D, Bellosta R, Attisani L, Pegorer M, Socrate AM, et al. Vascular Surgery During COVID-19 Emergency in Hub Hospitals of Lombardy: Experience on 305 Patients. European Journal of Vascular and Endovascular Surgery. 2021;61(2):306-15.
442. Behrendt C-A, Seiffert M, Gerloff C, L'Hoest H, Acar L, Thomalla G. How Does SARS-CoV-2 Infection Affect Survival of Emergency Cardiovascular Patients? A Cohort Study From a German Insurance Claims Database. European Journal of Vascular and Endovascular Surgery. 2021;62(1):119-25.
443. Hedou M, Carsuzaa F, Chary E, Hainaut E, Cazenave-Roblot F, Masson Regnault M. Comment on 'Cutaneous manifestations in COVID-19: a first perspective' by Recalcati S. J Eur Acad Dermatol Venereol. 2020;34(7):e299-e300.
444. Wang CJ, Worswick S. Cutaneous manifestations of COVID-19. Dermatol Online J. 2021;27(1).
445. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020;383(4):347-58.
446. Fox SE, Lameira FS, Rinker EB, Vander Heide RS. Cardiac Endotheliitis and Multisystem Inflammatory Syndrome After COVID-19. Ann Intern Med. 2020;173(12):1025-7.
447. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20(11):e276-e88.
448. Toubiana J, Cohen JF, Brice J, Poirault C, Bajolle F, Curtis W, et al. Distinctive Features of Kawasaki Disease Following SARS-CoV-2 Infection: a Controlled Study in Paris, France. J Clin Immunol. 2021;41(3):526-35.
449. Kadkhoda K, Laurita K. Antineutrophil cytoplasmic antibodies and their association with clinical outcomes in hospitalized COVID-19 patients. Cell Death Discov. 2021;7(1):277.
450. Jedlowski PM, Jedlowski MF. Coronavirus disease 2019-associated immunoglobulin A vasculitis/Henoch-Schönlein purpura: A case report and review. J Dermatol. 2022;49(1):190-6.
451. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370(6515).
452. Vlachoyiannopoulos PG, Magira E, Alexopoulos H, Jahaj E, Theophilopoulou K, Kotanidou A, et al. Autoantibodies related to systemic autoimmune rheumatic diseases in severely ill patients with COVID-19. Ann Rheum Dis. 2020;79(12):1661-3.
453. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-8.

454. National Institute of Health. Antithrombotic Therapy in Patients With COVID-19 2022 [updated 24.2.22. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/.
455. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19 2021 [updated 13.4.22. Available from: https://www.nice.org.uk/guidance/ng191/chapter/Recommendations.
456. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S11-7.
457. Nielsen ND, Rollins-Raval MA, Raval JS, Thachil J. Is it hyperfibrinolysis or fibrinolytic shutdown in severe COVID-19? Thromb Res. 2022;210:1-3.