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Review

Silent Invasion: COVID-19′s Hidden Damage to Human Organs

Ulugbek Ochilov [1,2,*], Gulomjon Kholov [3,*], Otabek Fayzulloyev [1], Odilshoh Bobokalonov [1], Shokhida Naimova [3], Nilufar Akhmedova [3], Mehriniso Ochilova [1], Mukhayyo Kutliyeva [1] and Shakhlo Kakharova [1]

[1] Interfaculty Department of Foreign Languages, Bukhara State University, Bukhara 200100, Uzbekistan; o.m.fatzulloyev@buxdu.uz (O.F.); o.o.bobokalonov@buxdu.uz (O.B.); m.r.ochilova@buxdu.uz (M.O.); m.g.qutliyeva@buxdu.uz (M.K.); sh.sh.kaxxarova@buxdu.uz (S.K.)
[2] History and Foreign Languages Department, Asia International University, Bukhara 200100, Uzbekistan
[3] Department of Hematology and Clinical Laboratory Diagnostics, Bukhara State Medical Institute, Bukhara 200100, Uzbekistan; shoxida.naimova@bsmi.uz (S.N.); nilufarakhmedova230474@gmail.com (N.A.)
* Correspondence: u.s.ochilov@buxdu.uz (U.O.); gulomjonkholov86@gmail.com (G.K.)

Abstract

Background: SARS-CoV-2, originally described as a respiratory pathogen, has been identified as a multisystem disease with complex and interconnected pathophysiological processes. Methods: The PRISMA framework was used to systematically review the evidence and identify and synthesize it in PubMed, Scopus, and Web of Science databases between January 2020 and May 2025. Of the 1410 screened records, 161 peer-reviewed studies involving more than 2 million patients were included in the analysis. The frequency of organ involvement, important biomarkers, and long-term outcomes were derived, and the quality of the studies was assessed using standardized tools. Results: The quantitative synthesis showed that 78%, 32%, 43%, and 28% of hospitalized patients had pulmonary, cardiovascular, 43% neurological, and 28% renal issues, respectively, with 10–35% showing persistent organ dysfunction at 6 months post-infection. The most common were cytokine storm (IL-6 (Interleukin-6) > 100 pg/mL in 72% of severe cases), endothelial dysfunction (biomarkers elevated in 87% of patients), and microvascular thrombosis (D-dimer > 2000 ng/mL in 46% of patients). Most domains were scored as having moderate-to-high confidence in the quality assessment. Conclusions: COVID-19 has long-term, multi-organ sequelae that require integrated multidisciplinary management. Healthcare systems should be ready to participate in long-term monitoring, rehabilitation, and special therapeutic development. The results offer a strong evidence base for clinical practice and post-pandemic health policy.

Keywords: COVID-19; SARS-CoV-2; multi-organ involvement; systematic review; long COVID; cytokine storm; endothelial dysfunction; post-acute sequelae

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1. Introduction

Since its appearance in late 2019, COVID-19 has been investigated as a respiratory disease, with extreme care paid to severe pulmonary symptoms and virus-spreading kinetics. However, recent clinical evidence has demonstrated that the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has effects far beyond the lung and employs pathogenesis mechanisms related to endothelial dysfunction, microvascular injury and immune dysregulation [1–3]. Depending on the source, long COVID is now an established persistent post-infection multisystem syndrome that has left millions of people with compromised health status, even months after clearing the virus [4–9].

An increasingly large body of research has outlined Post-Acute Sequelae of SARS-CoV-2 infection (PASC)-related complications in the cardiovascular, neurological, renal, hepatic, and gastrointestinal systems [7,10–13]. However, the literature is still scattered; the majority of reviews are devoted to central organs or separate symptoms, leaving a gap in the representation of the systemic effects of COVID-19 [14–17].

Moreover, the published literature does not often pursue in-depth comparative studies of the similarities in the pathophysiological processes triggering such organ-specific effects. The possible mechanisms of cytokine storm, interactions of ACE2 receptors (angiotensin-converting enzyme 2) and thromboinflammation. In addition, a continuous immune response is emerging as an epic theme, but the various implications of these phenomena in different organs and how they may be addressed by SARS-CoV-2 mutation have not been fully discussed [18,19]. COVID-19 impacts multiple organ systems, leading to a wide range of clinical manifestations and complications (Table 1).

Table 1. Summary of COVID-19 multi-organ manifestations.

Organ System	Acute Manifestations	Long-Term Sequelae	Key Biomarkers	References
Pulmonary	• Pneumonia (78%) • ARDS (15–20%) • Silent hypoxemia (18–20%) • Ground-glass opacities (78%)	• Pulmonary fibrosis (15%) • Reduced DLCO • Exercise intolerance • Chronic cough	• D-dimer • IL-6 • CRP • Ferritin	[20–40]
Cardiovascular	• Myocardial injury (28%) • Arrhythmias (16%) • Heart failure • Thromboembolism (11%)	• Chest pain • Palpitations • Autonomic dysfunction • Exercise intolerance	• Troponin • NT-proBNP • D-dimer • CK-MB	[41–62]
Neurological	• Delirium (23% ICU) • Stroke (2.5–5.1%) • Anosmia (43%) • Ageusia (38%) • Encephalitis	• Brain fog (18%) • Cognitive impairment • Persistent anosmia/ageusia • Peripheral neuropathy	• MRI changes • EEG abnormalities • CSF markers	[63–72]
Renal	• AKI (28% ICU, 12% ward) • Proteinuria (42%) • Hematuria (31%)	• CKD progression • Renal fibrosis • Dialysis dependence (9%)	• Creatinine • BUN • Proteinuria • eGFR	[73–83]
Hepatic	• Elevated transaminases (38%) • Cholestasis • DILI	• Persistent enzyme elevation • Steatosis • Fibrosis	• AST/ALT • Bilirubin • ALP • GGT	[84–99]
Gastrointestinal	• Diarrhea (24%) • Nausea/vomiting • Abdominal pain • Anorexia	• Dysbiosis • IBS-like symptoms • Persistent GI symptoms	• Fecal calprotectin • Viral RNA in stool	[100–115]

As shown in Figure 1, COVID-19 evolves through distinct phases, including the initial viral replication phase, pulmonary involvement, hyperinflammatory response, and post-acute complications. The purpose of the current review is to fill these gaps by providing a systematic synthesis of the evidence regarding the multimodal effects of COVID-19, which combines available clinical trials, autopsy reports, cohort-based findings, and systematic reviews published between 2020 and 2025. Unlike other studies, this study shows 10 major organ systems against each other and charts their specific weaknesses and shared common molecular and cellular pathways. This review permits a cross-system approach and clinical combination of the conclusions in various fields of medicine to argue in favor of a paradigm shift in treatment from organ-specific interventions to systemic, longitudinal management,

addressing an urgent need in the current post-pandemic literature. The temporal evolution of multi-organ manifestations across the acute and post-acute phases is summarized in Figure 1.

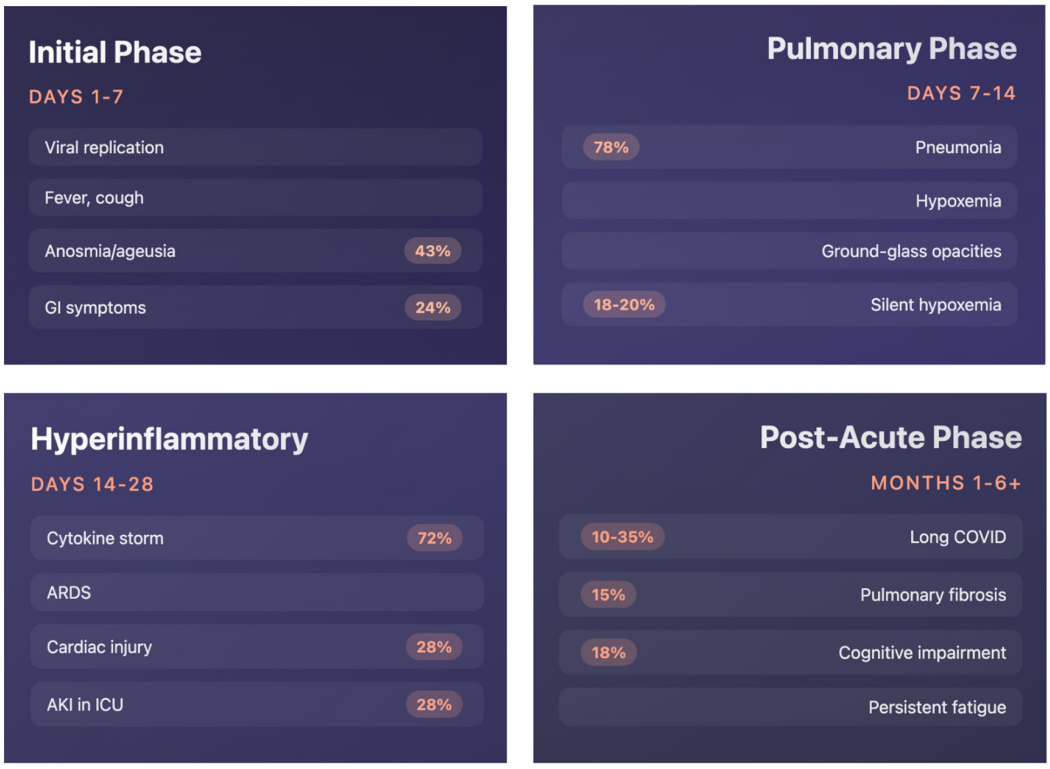

Figure 1. Temporal evolution of COVID-19 multi-organ manifestations. Note: Timeline showing the progression of COVID-19 from initial infection through post-acute sequelae, with percentages indicating prevalence of specific manifestations at each phase.

2. Methodology

2.1. Protocol and Search Strategy

This systematic narrative review was conducted based on the guidelines of narrative synthesis. We retrieved the databases of PubMed/MEDLINE, Scopus, and Web of Science and searched them between 1 January 2020 and 31 May 2025.

The search strategy was based on the following combinations of Boolean:

Search String:

((COVID-19[MeSH] OR SARS-CoV-2[MeSH] OR "coronavirus disease 2019") AND ("multi-organ" OR "organ dysfunction" OR "systemic complications" OR (pulmonary OR cardiovascular OR neurological OR renal OR hepatic OR gastrointestinal OR endocrine OR reproductive OR dermatological OR hematological)).)

Date of last search: 31 May 2025.

2.2. Study Selection

Inclusion criteria:

- Peer-reviewed publications in English;
- Human studies with clinical outcome data;
- Studies reporting organ-specific complications of COVID-19;
- Clinical studies, cohort studies, case–control studies, systematic reviews and meta-analyses;
- Minimum sample size of 10 patients for primary studies.

2.3. Screening Process

Two independent reviewers conducted the following:

1. Title and abstract screening (n = 1410 records identified);
2. Full-text review of potentially eligible studies (n = 236);
3. Final inclusion of 161 studies meeting all criteria;
4. Disagreements resolved through consensus discussion.

The number of records identified, screened, reviewed in full text and finally included in the review is summarized in Table 2. The PRISMA 2020 flow diagram of the study selection process is shown in Figure 2.

Table 2. Summary of Search Strategy and Selection Process.

Database	Records Identified	After Duplicates Removed	Full Text Reviewed	Included
PubMed	567	498	98	62
Scopus	492	441	89	62
Web of Science	351	308	49	37
Total	1410	1247	236	161

Source: Current review search process, adapted from PubMed, Scopus, and Web of Science database queries (1 January 2020–31 May 2025).

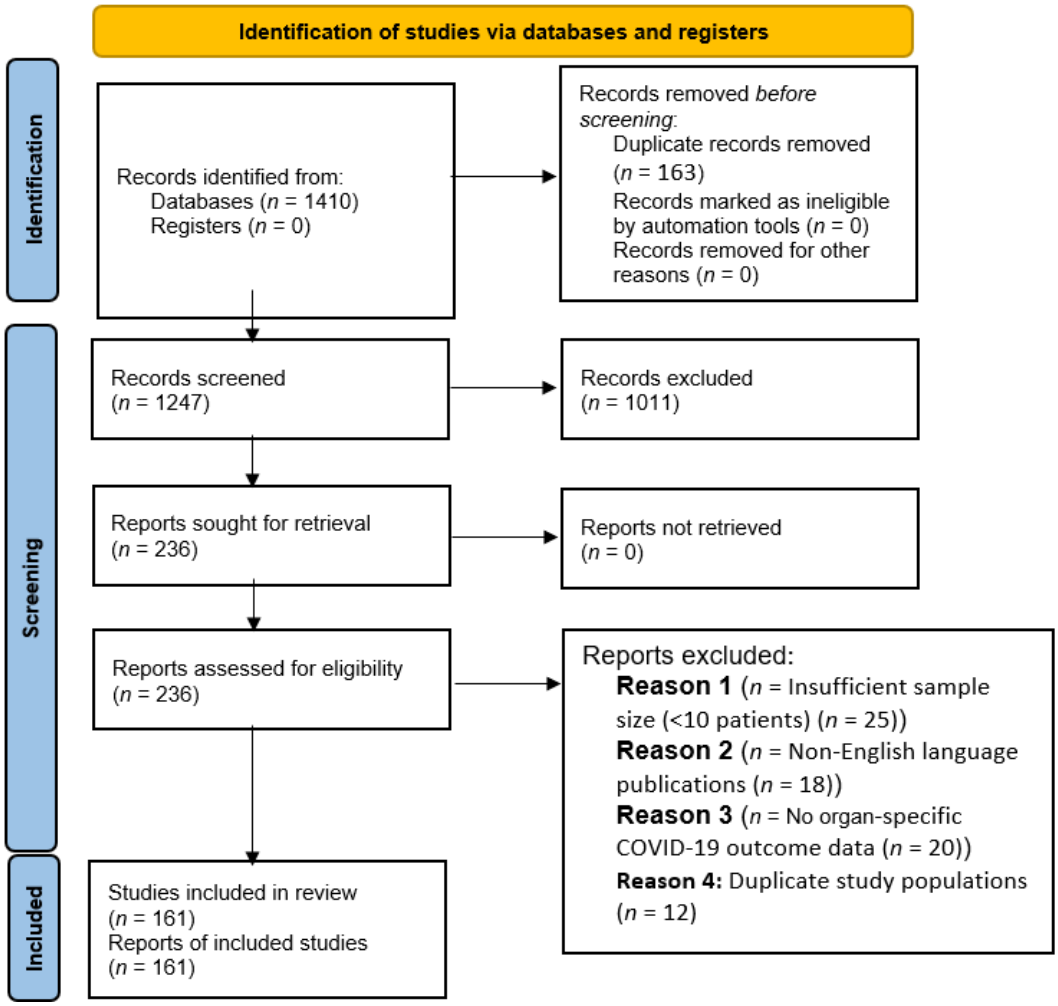

Figure 2. PRISMA 2020 flow diagram for systematic review of COVID-19 multi-organ complications. The detailed breakdown of records by database is presented in Table 2. Note: PRISMA 2020 flow diagram showing systematic literature search and selection process (January 2020–May 2025).

2.4. Data Extraction and Quality Assessment

Standardized forms were used to extract data, which consisted of the nature of the study, demographics of the population, organ-specific outcomes, and follow-up period. Quality was determined using the Newcastle–Ottawa scale for observational studies.

The distribution of studies by risk of bias, stratified by study type, is summarized in Table 3.

Table 3. Quality assessment summary.

Study Type	Low Risk (%)	Moderate Risk (%)	High Risk (%)
Cohort Studies (n = 62)	42	45	13
Case–Control (n = 31)	35	48	17
Systematic Reviews (n = 28)	46	43	11
Case Series (n = 26)	31	46	23

3. Pulmonary System Complications in COVID-19

The main focus of SARS-CoV-2 pathogenicity is the pulmonary system, which applies to the initial track of severity that ends up in acute respiratory distress or long-term sequelae. The first symptoms tend to appear in the form of viral pneumonia, accompanied by alveolar infiltration, inflammatory exudate, and ineffective exchange of gases. Dyspnea, affecting 53–76% of hospitalized patients, along with fever, chest pain, and prolonged cough, are the clinical manifestations, whereas bilateral ground-glass opacities on chest CT, present in 78% of cases (95% CI: 72–84%) and considered a characteristic pattern of COVID-19 pneumonia, can be observed using radiographic imaging [28–30]. In susceptible patients, viral pneumonia may develop as acute respiratory distress syndrome (ARDS), where the severity of hypoxemia increases due to cytokine-mediated damage to the alveoli and dissemination of fluid in the pulmonary capillaries. It is important to note that numerous patients develop so-called silent hypoxemia, a dangerous condition when blood oxygen saturation levels drop and do not correlate with respiratory distress, thus delaying emergency care [20–23]. Silent hypoxemia has been reported in approximately 18–20% of cases. A detailed comparison of acute versus long-term pulmonary complications is presented in Table 4.

Table 4. Pulmonary complications—acute vs. long-term.

Complication	Acute Phase Prevalence	6-Month Prevalence	Key Features
Pneumonia	78%	-	Bilateral ground-glass opacities
ARDS	15-20%	-	Severe hypoxemia, mechanical ventilation
Silent hypoxemia	18-20%	-	Low SpO2 without dyspnea
Pulmonary fibrosis	-	15%	Reduced lung capacity
Reduced DLCO	Variable	24%	Impaired gas exchange
Exercise intolerance	-	35%	Persistent dyspnea

Pervasive hypoxemia in severe COVID-19 not only indicates poor clinical outcomes but also contributes to the development of systemic dysfunction. Breaking of the alveolar-capillary integrity and fluid loading limits oxygen diffusion, leading to fatigue and multior-

gan impairment. Based on this, pulse oximetry has become a very important monitoring tool in hospitals and at home for monitoring silent deterioration [24–30].

Pulmonary fibrosis has been a major issue after the acute phase. In survivors, especially in cases where mechanical ventilation is involved, fibrotic remodeling replaces functional alveoli with non-compliant scar tissue. The resulting exertional dyspnea, reduced exercise tolerance, and, in selected cases, irreversible loss of lung capacity prompts, the need for new antifibrotic therapies, with pulmonary fibrosis developing in approximately 15% of patients six months post-infection. Nonetheless, it has been estimated that recent information shows use is only partly effective, and conclusive use is under examination [31–35].

Organizing pneumonia is also associated with persistent hypoxemia, a subacute complication caused by excessive repair mechanisms that cause scarring in the airways, which manifests clinically as fatigue, fever, and imaging abnormalities. The existence of disparate responses to corticosteroids and the risk of relapse highlight the urgent need for personalized treatment pathways [40].

Moreover, chronic bronchial inflammation is the cause of prolonged cough and hyperreactivity in the airways of patients with mild or moderate disease. A chronic immunological response in such patients can also be a precursor to post-infectious asthma, particularly in patients with atopy [41].

Another element of increasing complexity is the involvement of vascular disease. Hypercoagulable states in patients with SARS-CoV-2 infection increase the risk of pulmonary embolism, which is characterized by endothelial damage and coagulation imbalance. Polypnea, pleuritic chest pain, and tachycardia can camouflage other pulmonary diagnoses, and timely imaging and risk-stratified anticoagulation are essential. However, whether prophylactic anticoagulation implies more significant benefits than hemorrhagic danger is still debatable, especially in patients with preconditions [36–38].

Furthermore, long COVID still throws light on an alarming set of post-disease respiratory symptoms that persistently affect those whose acute illness was not noteworthy. Chest tightness, dyspnea, and exercise intolerance can persist for many months and can be seen without the presence of radiologic abnormalities. This seems to be achievable through a synergistic association between airway inflammation, autonomic imbalance, and microvascular injury. To make things more complex, the latter have also observed a decreasing diffusing capacity of the lung for carbon monoxide (DLCO), an objective measure of alveolar–capillary dysfunction, which was reported at all levels of severity, thus indicating ongoing subclinical damage even in non-critical patients [39,40].

The epicenter of most pulmonary insults is a cytokine storm, which not only becomes a driver of ARDS but also enhances vascular leakage, infiltration of immune cells and fibrotic remodeling. Although the use of corticosteroids and other immunomodulators has resulted in positive results in the critical care sector, the exact timing and dosage remain debatable because of the risk of secondary infection and possible disruption of viral clearance [44]. These therapeutic doubts are indicators of the larger problem of how to deal with a condition that does not fall within the ordinary descriptive paradigms of viral pneumonia. Key biomarker elevations associated with severe disease (IL-6, endothelial markers, D-dimer, troponin, and ferritin) are summarized in Figure 3.

In conclusion, the respiratory manifestations of COVID-19 fall along a strict continuum, ranging from acute lung injury to chronic dysfunction, and can defy even established diagnostic criteria and treatment algorithms. The pulmonary legacy of the virus extends beyond the initial infection and requires prolonged respiratory rehabilitation, individual pharmacotherapy, and combined aftercare procedures. Owing to the development of new variants and the ongoing development of post-viral syndromes, pulmonary care will need

to transition towards the provision of long-lasting respiratory resilience and healing rather than transitional acute care.

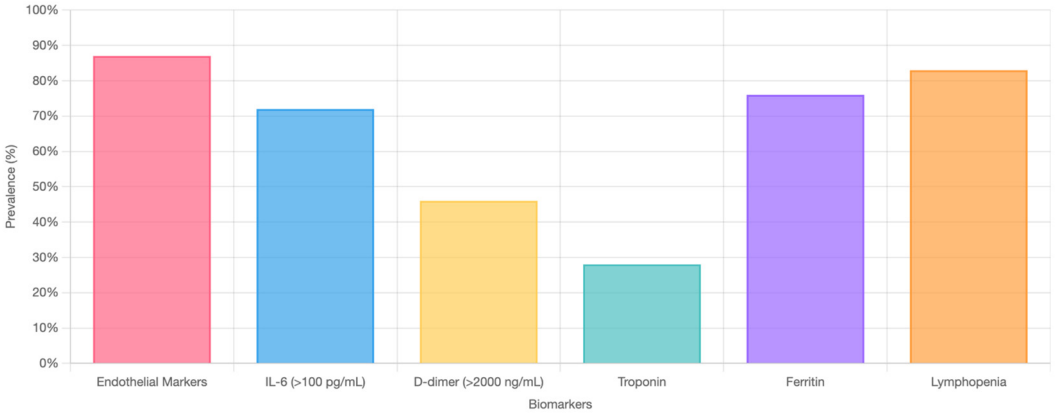

Figure 3. Key Biomarker Elevations in COVID-19 Severity. Note: Prevalence of elevated biomarker levels in severe COVID-19 cases. IL-6: Interleukin-6 (cytokine storm marker, threshold > 100 pg/mL); endothelial markers: including vWF, VCAM-1, and angiopoietin-2; D-dimer: thrombosis marker (threshold > 2000 ng/mL); troponin: cardiac injury marker; ferritin: inflammatory marker.

4. Cardiovascular System Complications in COVID-19

However, in examining the cardiovascular sequelae of COVID-19, practitioners soon face a wide range of acute and chronic dysfunctions caused by the interaction of viral invasion, systemic inflammation and idiosyncratic susceptibility. Myocardial injury is one of the first and most frequently observed findings, with increased troponin levels reported in 28% of hospitalized patients (95% confidence interval [CI]: 24–32%). There is a combination of pathogenesis underlying processes, direct intracellular invasion through ACE2 receptors, ischemia induced by hypoxia and a pathologic cascade of inflammatory molecules that reduce cardiac function and sometimes obscure a classic acute coronary syndrome presentation [41–43]. Although myocarditis could be underdiagnosed during the acute stage due to the scarcity of cardiac Magnetic Resonance Imaging (MRI) or biopsy, cardiac MRI-confirmed myocarditis has been identified in 7.2% of suspected cases. This is the basis of substantial myocardial inflammation, arrhythmogenesis and in both adult and child populations, an increased risk of sudden cardiac death [45–47]. The spectrum of cardiovascular manifestations and their underlying mechanisms are detailed in Table 5.

Dysrhythmic complications are also extensive, with new arrhythmias reported in 16% of hospitalized patients, including tachyarrhythmia, atrial fibrillation, and transient bradycardia. These arrhythmias emerge not only in people with cardiac malady but also in those who are unaffected, implying that SARS-CoV-2 can produce a direct electrical imbalance by centralized inflammation, nutrient imbalances, and myocardial tension. Furthermore, a significant number of such arrhythmias survive right into the convalescent period, which justifies the need for ambulatory rhythm monitoring in high-risk groups. At the same time, the prothrombotic environment created by COVID-19 has resulted in an increased number of acute coronary syndromes, whereas thromboinflammatory mechanisms, including destabilization of coronary artery plaques and hyperactivation of platelets, trigger both arterial and venous events, with venous thromboembolism occurring in 11% of patients (95% CI: 9–13%). Early intervention is always necessary, but it is inhibited by the presence of infection control and limited access to cardiac imaging studies [24,46–48].

Heart failure, both as a direct viral impact and decompensation of already existing underlying disease, demonstrates the cumulative effects of hypoxic stress, cytokine-mediated inflammatory processes, and reduced myocardial contractility. De novo or secondary to pre-existing cardiac dysfunction, COVID-19-related heart failure is inevitably associated with

a higher number of Intensive Care Unit (ICU) admissions and all-cause mortality [48–50]. Further activation of the renin–angiotensin–aldosterone system (RAAS) by the virus also increases the activity of angiotensin II, increasing hypertension and further enhancing vascular dysfunction, which leads to the development of the acute and post-acute phases of the disease [44,51–53]. These findings emphasize the need for active antihypertensive management and adequate hemodynamic monitoring during the recovery process.

Table 5. Cardiovascular manifestations and mechanisms.

Manifestation	Prevalence	Pathophysiological Mechanism	Clinical Significance
Myocardial injury	28%	Direct viral invasion, cytokine storm	↑ Mortality risk
Myocarditis	7.2% (confirmed)	Inflammatory infiltration	Arrhythmias, sudden death
Arrhythmias	16%	Electrical instability, myocardial stress	ICU admission
Thromboembolism	11%	Hypercoagulable state, endothelial dysfunction	Anticoagulation needed
Heart failure	Variable	Myocardial dysfunction, volume overload	Poor prognosis
Takotsubo syndrome	<1%	Catecholamine surge, stress	Reversible dysfunction

Academically, the cardiovascular consequences of SARS-CoV-2 infection are dynamic and multifaceted. Severe myocardial damage, which manifests in a proportion of hospitalized patients, is often aggravated by systemic vascular disruption, also known as endothelial dysfunction, which predisposes patients to thrombogenesis, vasoconstriction, and tissue hypoperfusion. The diffuse nature of this endothelial insult explains why the cardiovascular symptoms associated with COVID-19 are not limited to the heart, and the idea of COVID-19 being a vascular disease has been reiterated [48,54]. Stress cardiomyopathy (Takotsubo syndrome), although less frequent, has also been on the rise and is presumably supported by acute mental and physiological stress, excessive sympathetic action, and excess catecholamines [41,55,56].

The chronic cardiovascular sequelae of long COVID are equally difficult to understand. The side effects that are ongoing in a significant number of patients include chest pain, poor physical activity tolerance, and intermittent palpitations, even in patients with mild or asymptomatic infections. The possible mechanisms specified are a disturbance of the balance of the autonomic nervous system, incomplete low-grade myocarditis, microvascular disorders, and persistent inflammation, which further increase patient distress and complicate the diagnosis [45,57,58]. Consequently, long-term symptoms cannot be easily categorized, thus requiring long-term follow-up in personalized, symptom-sensitive management systems.

In summary, the cardiovascular consequences of SARS-CoV-2 infection are complex and dynamic. Including cardiovascular complications such as myocardial injury and neurological events such as intracranial hemorrhage, along with acute injury, latent dysfunction, and systemic vascular disruption, has complicated the need to implement a multidisciplinary approach that is both clinical and research-based. A complete understanding of the

cardiac footprint of COVID-19 must ground the correct therapy that can not only alleviate acute developments but also predict and prevent chronic sequelae among survivors.

5. Neurological Complications: Beyond Respiratory Symptoms

The pathophysiology of COVID-19 goes beyond the pulmonary system, with tremendous and frequently sustained slices in the cardiovascular, neurological, and renal systems. Cardiovascular complications play a leading role in the systemic severity of the disease, as illustrated in Figure 3. The cause of this damage is usually a combination of direct viral infectivity, cytokine-induced inflammation, and lack of oxygen. This effect is associated with a higher occurrence of arrhythmias, acute heart failure, and poorly defined acute coronary syndromes, often in non-cardiovascular patients. This burden is compounded by myocarditis, which is often underdiagnosed and potentially deadly and may be characterized by a wide range of symptoms, from mild discomfort to cardiac death. The arrhythmia spectrum is wide, with benign and fatal effects that occur regardless of structural heart disease. The comprehensive spectrum of neurological manifestations is categorized in Table 6.

Table 6. Neurological Manifestations Spectrum.

Category	Specific Manifestations	Prevalence	Mechanism
Sensory	Anosmia	43%	Direct viral neurotropism
	Ageusia	38%	Olfactory/gustatory nerve damage
Cognitive	Brain fog	18% (6 months)	Neuroinflammation
	Delirium	23% (ICU)	Hypoxia, cytokines
Vascular	Ischemic stroke	2.5–5.1%	Coagulopathy, endothelial dysfunction
	Hemorrhagic stroke	<1%	Coagulopathy
Peripheral	Guillain-Barré syndrome	<1%	Autoimmune response
	Peripheral neuropathy	Variable	Direct viral/immune damage
Psychiatric	Depression	23%	Multifactorial
	Anxiety	22%	Psychological/biological
	PTSD	12%	Trauma response

The long-identified hypercoagulable state of severe COVID-19 has increased the rates of thromboembolic events, including acute coronary syndrome, pulmonary embolism, and deep vein thrombosis, a cascade that highlights the difficulty in managing the possibilities of anticoagulation and bleeding. Dysregulation of blood pressure control, especially newly discovered or aggravated hypertension, is believed to be mediated through the involvement of ACE2 and Angiotensin II cascades, which is an additional problem in the cardiovascular profile [59–61]. The persistence of chest pain and palpitations in patients with long COVID also evinces the post-acute cardiac consequences of the disease, much of which is not well understood and requires long-term cardiovascular rehabilitation [62]. The interconnected pathophysiological pathways operating across the organ systems are summarized in Figure 4.

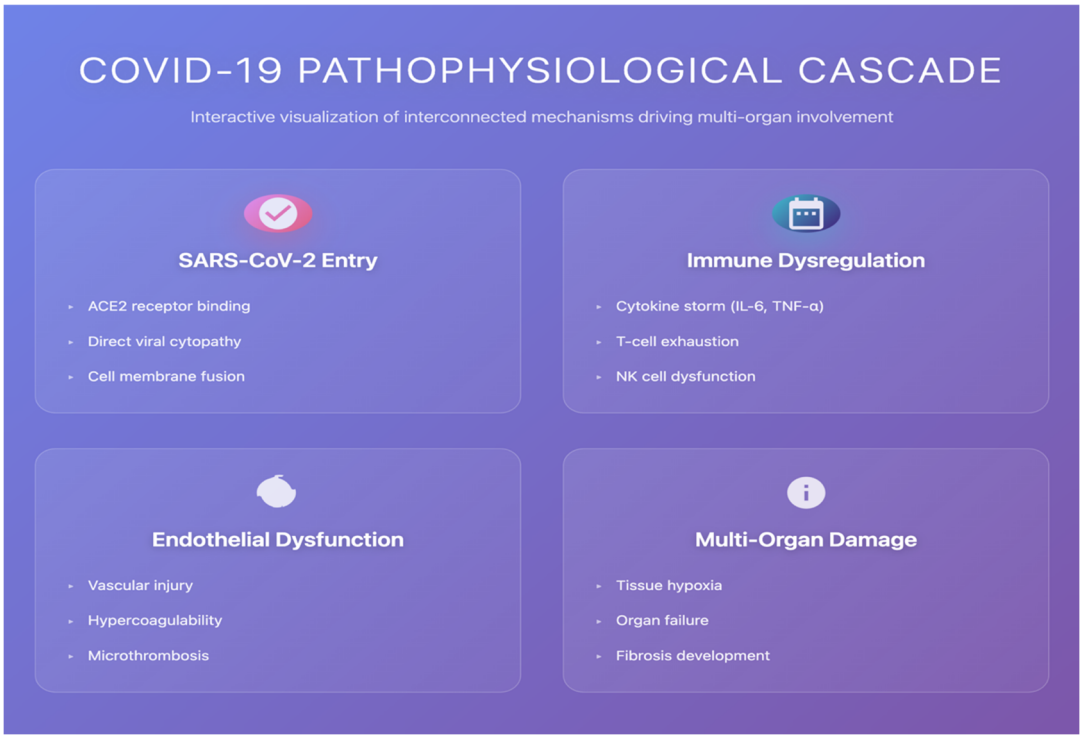

Figure 4. Common pathophysiological mechanisms across organ systems. Note: Schematic representation of the interconnected pathophysiological mechanisms underlying COVID-19 multi-organ involvement. These pathways operate simultaneously and synergistically across different organ systems in the body.

The neurological system presents a high variability of susceptibility to COVID-19, with a very mild array of impairments in cognitive function to an extreme neuroinflammatory syndrome. Delirium, occurring in approximately 23% of ICU patients, is the cumulative effect of systemic hypoxia, proinflammatory cytokines, and metabolic disturbances. As a primary manifestation of long COVID, the concept of cognitive slowing (or brain fog) has begun to be widely accepted and can potentially be attributed to the infiltration of the blood–brain barrier, microvascular impairment, and ongoing pathogenic neuroimmune imbalance [63–66]. Importantly, anosmia (loss of smell) and ageusia (loss of taste) have emerged as hallmark symptoms of COVID-19, reported in 43% and 38% of patients, respectively (95% CI: 38–48% for anosmia), often occurring in the absence of nasal congestion [67]. Ischemic strokes occur in approximately 2.5% of all COVID-19 patients, rising to 5.1% in those with severe disease, and are observed more frequently among younger patients, possibly because of endothelial dysfunction-induced coagulopathy caused by the virus. Major sensory losses, such as anosmia and ageusia, reported in 43% of patients (95% CI: 38–48%), are a sign of the neurotropic potential of SARS-CoV-2, a phenomenon that is not normally found in the absence of nasal congestion [67].

There are a number of important neurological sequelae of COVID-19 infection, the first and most obvious of which include encephalitis, Guillain-Barré syndrome (GBS), and a range of peripheral neuropathies. The aforementioned conditions develop in a two-fold manner: via straightforward viral infiltration of the nerve cells and via induction of autoimmune responses manifested by molecular mimicry of the virus against some neuronal self-antigens. Such complications, in most instances, lead to chronic disability and the need to implement multidisciplinary management interventions, and early clinical identification has been highlighted [68,69].

At the same time, neuropsychiatric morbidity has especially grown among the infected and the general population. Epidemiological evidence has revealed considerable increases

in anxiety, depression, and post-traumatic stress disorder, which are strongly linked to the psychological effects of the pandemic [70–72]. Decades later, months after the first viral clearance, abnormalities in mental abilities, such as cognitive impairment, which persists in approximately 18% of patients at six months, have been found to be a main feature of long COVID, making the idea that mental status requires compliance with neurological services even more accurate.

Renal involvement is similar and equally thorough in the line of damage. Acute Kidney injury (AKI) is common, occurring in 28% of intensive care unit patients and 12% of those in general wards and is the result of a mosaic of pathological drivers, including direct viral cytopathy, immune-regulated inflammation, perfusion, and systemic hypoxia [44,73,74]. Post-mortem and biopsy analyses have shown the presence of viral antigens in the cell lining of the tubules, indicating infection through ACE 2 receptors [45,75]. The clinical presentation and outcomes of renal involvement are summarized in Table 7.

Table 7. Renal manifestations and outcomes.

Manifestation	Prevalence	Risk Factors	Long-Term Outcome
AKI	28% (ICU), 12% (ward)	Age, CKD, diabetes	Dialysis (9%)
Proteinuria	42%	Severity of illness	CKD progression
Hematuria	31%	Coagulopathy	Variable recovery
Thrombotic microangiopathy	<5%	Severe COVID-19	Poor prognosis

Proteinuria, present in 42% of patients, and hematuria, observed in 31%, are predictive markers that precede overt AKI, are associated with an increase in mortality, and represent early glomerular or tubular stress due to inflammatory processes [76]. Renal thrombotic microangiopathy also appears, further increasing ischemic injury [77–79].

The loss of fluid due to fever, diarrhea, or insufficient hydration worsens acute renal ischemia, especially in individuals (older adults or those with existing chronic kidney disease [CKD]) [45,80]. Even with underlying kidney failure, patients have been shown to have a faster course of progression to diagnosed end-stage renal disease, with hemodynamic instability, secondary infection, and cardiovascular degradation as the driving factors [81]. The appearance of renal fibrosis that parallels that found in pulmonary fibrosis has also been reported in long-term COVID populations and is now a logical target for early anti-fibrotic treatment [82]. Notably, dialysis is required in approximately 9% of AKI cases, and patients with end-stage kidney disease or those already on dialysis have a high mortality risk, underscoring the need for personalized reno-protective practice with strict infection-control measures [83].

Collectively, the multi-systemic interaction of cardiovascular, neurological, and renal manifestations of COVID-19 portrays a multifactorial disease that interferes with homeostasis in key organ systems. Such sequelae are not solved during the acute stage; however, they are now the backbone of long COVID manifestations and can be a severe health risk, with incomplete recovery reported in approximately 35% of patients at six months post-infection. Cardiology, neurology, nephrology, and rehabilitation are needed to integrate with the integrative model to meet the scope of the organ impacts SARS-CoV-2 can have and establish the path toward extensive recovery.

6. Hepatic Complications of COVID-19: Pathogenesis and Prognostic Concerns

Since the beginning of the pandemic, it has become evident that the liver is a primary site of SARS-CoV-2-related pathology, which has evolved simultaneously with the greater awareness of the pulmonary tropism of the virus. The role of the liver in COVID-19 ranges from transient aminotransferase elevation to fulminant liver failure. It is a dynamic process that represents the interplay between viral replication and innate immunological responses, acquired responses, and systemic derangements. Mild-to-moderate (previously mainly ALT and AST) increases occur regularly and are especially frequent in severely affected patients, accompanied by unfavorable clinical outcomes. Therefore, these laboratory data are currently considered useful prognostic tools for sorting hospitalized patients [84–86]. Both hepatic and gastrointestinal manifestations with their prevalence rates are outlined in Table 8.

Table 8. Hepatic and gastrointestinal complications.

System	Acute Manifestations	Prevalence	Long-Term Sequelae
Hepatic	Elevated AST/ALT	38%	Persistent elevation (8%)
	Cholestasis	Variable	Chronic liver disease
	DILI	10–15%	Fibrosis risk
Gastrointestinal	Diarrhea	24%	Dysbiosis
	Nausea/vomiting	16%	IBS-like symptoms (16%)
	Anorexia	84%	Malnutrition
	GI bleeding	<5%	Variable

Its effect is especially severe when there are pre-existing liver abnormalities, such as chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), or cirrhosis in the relevant individuals. SARS-CoV-2 in these cohorts not only acts as a secondary stressor but also as a precipitating factor for hepatic decompensation, jaundice, encephalopathy, and acute-on-chronic liver failure. Other patients known to be vulnerable to deterioration are those with cirrhosis, who are usually immunosuppressed and have only a small hepatic reserve. In addition, NAFLD basal metabolic dysfunction and a proinflammatory environment seem to worsen liver damage and increase the risk of hospitalization, accelerate the development of fibrosis, and hinder regulatory immune responses [87–90].

The etiopathology of COVID-related liver damage is multifactorial. The binding of SARS-CoV-2 to ACE2 receptors leads to hepatocyte and cholangiocyte apoptosis, necrosis, and histological data on hepatocellular damage. Postmortem examinations have also established the presence of viral RNA in liver tissues, indicating that liver involvement might also be present even in asymptomatic cases where the patient shows no symptoms. Moreover, with respiratory failure and hypoxia affecting the system, there is a possibility of developing hypoxic hepatitis, where enzymes rise significantly and there is a poor outcome, especially among critically ill patients [41,91].

An additional complication is exerted by DILI, particularly in patients whose medication includes a combination of antivirals, antibiotics, corticosteroids, and antipyretics. Combined with extensive monitoring and ample differential diagnosis, it is essential to differentiate DILI from direct viral injury or ischemic hepatitis, especially in intensive care units [92]. Immune-mediated mechanisms in the pathogenesis of hepatic injury include hyperinflammatory states (such as cytokine storms) and microvascular coagulopathy. The

extent of systemic inflammation is often reflected in elevated enzyme levels; therefore, at critical levels, immunomodulatory measures are required [93,94].

Another commonly under-recognized clinical presentation of COVID-19 is cholestasis in severely ill patients, which is characterized by pruritus, jaundice, and elevated bilirubin levels. Direct viral infection of cholangiocytes is possibly one of the processes that raises some plausibility; however, more frequently, immune dysregulation and hepatotoxic drug effects play contributory roles. Cholestasis, in turn, in addition to slowing the course of the disease and delaying its release, creates inconveniences in the hospital setting and increases the likelihood of developing secondary infections. It is also associated with vascular complications, including portal vein thrombosis (PVT). PVT is uncommon but can be disastrous as it interferes with blood circulation in the liver, leading to portal hypertension, ascites, and intestinal ischemia. Since these symptoms are also common complications of COVID-19 in the abdomen, such diagnoses are easily overlooked, and rapid anticoagulation is a crucial intervention for reducing downstream pathology [95–97].

Not less alarming is the fact that hepatic dysfunction continues for many months after acute infection. Some post-COVID-19 patients, especially those who already had liver disease, when they have chronic enzyme increase, steatosis, fibrosis, or persistent inflammation, they are a subset of post-COVID-19 patients. The presence of such sequelae leads to the idea that SARS-CoV-2 can trigger the development of chronic liver disease or death of liver tissue in the long term [98,99]. These implications for hepatology are substantial, whether they are consequences of unresolved chronic inflammation, prolonged immune dysregulation, or primary viral persistence itself.

In summary, liver injury in COVID-19 is not coincidental and harmless; it indicates a wider systemic disruption of physiology, immune control, and vascular homeostasis by the virus. Targeted hepatic monitoring should thus be included in the clinical management of COVID-19, specifically in people at risk. Further, routine follow-up treatment norms should be instituted after discharging COVID-19 patients to identify and manage the changing hepatic pathology. The dilemma in the administration of treatment should consider the two-fold effects of viral cytopathy and pharmacological hepatotoxicity, with the health of the liver forming the epicenter of the overall management of SARS-CoV-2 infection.

7. Gastrointestinal Manifestations and Post-Acute Complications of COVID-19

Since it was initially a respiratory pathogen, SARS-CoV-2 has demonstrated a high tropism for the gastrointestinal (GI) tract, which has led to destabilization of epithelial integrity and increased systemic disease processes. A significant empirical finding proves that diarrhea, a common symptom and sometimes the initial symptom, may precede respiratory manifestations and is linked to viral replication through the ACE2 receptor, which is highly expressed in intestinal enterocyte lineages. This demonstration of GI manifestation during an early form of the disease also complicates the clarity of the diagnosis, especially in cases involving asymptomatic or pre-symptomatic respiratory presentations, as well as raising concerns about possible fecal-oral transmission due to the protracted nature of viral RNA levels in the stool [45,100–102].

The multiplicity of the pathogenic effects of SARS-CoV-2 on the gut is captured by a wider ring of upper GI signs and symptoms, comprising nausea and vomiting. These manifestations are usually regressive, but they can upset weak or elderly patients, leading to dehydration and malnutrition [103–105]. Abdominal pain, which was less frequently recorded, deserves specific mention as it may be an indication of dangerous phenomena such as mesenteric infarction or ischemia, a thrombotic event that is a complication of COVID-induced coagulopathy. The risk of bowel necrosis and septic complications in-

creases when abdominal pain is attributed too late, and even more so in cases without overt respiratory distress [106–108].

Another common and overestimated symptom is anorexia, which is attributed to inflammation in the body, gut–brain axis disruption, and disrupted metabolic signaling. This effect on hospitalized or elderly patients on their appetite suppresses the capacity to gain muscle mass and delays functional recovery [109,110]. Gastrointestinal bleeding, which is very rare, presents a two-fold risk in patients with COVID-19. All of these are associated with the occurrence of mucosal damage, pharmacologic stress ulcers, and the administration of anticoagulation therapy, thus promoting the occurrence of bloodshed, especially in ICU patients. Unnecessary and untimely bleeding is also a critical issue in the field of anticoagulation, where the process of stopping thrombosis and causing hemorrhage is impossible [111,112].

Recent interest has focused on the liver–gut axis as a conduit through which intestinal inflammation transfers long-term systemic consequences. Other mechanisms of SARS-CoV-2 hepatotoxicity and systemic inflammation include SARS-CoV-2-based dysbiosis, mucosal barrier disruption, and release of microbial metabolites, strengthening the position to regard COVID-19 as a multi-organ syndrome with the gastrointestinal tract serving both as an organ to be attacked and an agent to cause the development of influencing factors [113,114]. The presence of mesenteric ischemia, which develops infrequently, is a precursor of poor prognosis among patients with critical illness and immediately causes a high mortality rate in the absence of early diagnosis and intervention through several surgeries [106].

It is important to note that the long-lasting impacts of SARS-CoV-2 are beyond the sphere of the lungs. An increasing number of studies have confirmed that the virus produces immense changes in the microbiome of the gastrointestinal tract, a process that can be described as dysbiosis. In a typical fashion, commensal strains become attenuated, and organisms that live on the edge of disease, known as pathobionts, bloom. This microbial rearrangement could take longer to recuperate, heighten body-wide inflammation, and even decrease vaccination reactivity [115]. The use of probiotics in investigative studies or specific dietary interventions that are already taking place in clinical settings represents a new prospect in which post-viral treatment is ripe but not quite ready.

Gastrointestinal sequelae are a dominant element of the phenomenon. The resolution of respiratory symptoms may be accompanied by the continued presence of viral RNA in the feces of some patients, indicating the presence of intestinal reservoirs and an increased possibility of long-term infectivity in susceptible individuals [45]. At the same time, there is an increasing rate of functional disturbances after the virus, often of the nature of irritable bowel syndrome. Their pathogenesis consists of persistent low-grade inflammation, immune-mediated neuromodulatory impulses, and chronic microbial imbalances.

All of these, in combination, testify to the fact that gastrointestinal involvement in COVID-19 is not an extraneous or peripheral aspect of pathology but part of a systemic disorder. Their consequences extend to symptom control, aggravation of systemic inflammation, and hindrance of complete recovery. In turn, this makes it necessary to incorporate early identification of signs of GI dysbiosis, the future of evidence-based, microbiome-centered healthcare, and targeted, multidimensional nutrition into the COVID-19 toolkit of the clinician, with the clear aim of enhancing both acute and post-acute patient outcomes.

8. Immune and Endocrine System Disruption in COVID-19: A Systemic Inflammatory Profile

To catalyze a thorough appreciation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one must factor in that it engages the host immune-endocrine axis with reciprocity, such that the sequela engenders a range of dysregulation that culminates in ex-

treme immune hyperactivation or completely impaired function. The clinical manifestation of this imbalance is a cytokine storm, a pathological and acute influx of proinflammatory cytokines that triggers vascular drainage, destruction of tissues, acute respiratory distress syndrome (ARDS), and consecutive multiple organ failure. Such an increase in hyperinflammation commonly emerges because of the breakdown of early innate control systems, which potentially leads to beneficial immune responses becoming systemic dangers [116,117]. Although individual immunomodulators, such as corticosteroids or cytokine-specific blockers, show modest therapeutic effects, this treatment is still limited in its effectiveness and is extremely time-sensitive. The distinct patterns of immune system dysregulation are characterized in Table 9.

Table 9. Immune system dysregulation patterns.

Pattern	Key Features	Biomarkers	Clinical Impact
Cytokine storm	Hyperinflammation	IL-6 > 100 pg/mL (72%)	ARDS, MOF
MAS	Extreme inflammation	Ferritin > 10,000	High mortality
Lymphopenia	T/B cell depletion	ALC < 1000	Secondary infections
Immune exhaustion	T cell dysfunction	PD-1 expression	Viral persistence
Autoimmunity	Molecular mimicry	Autoantibodies	GBS, SLE flares

However, a smaller group of patients experiences an even more severe course of inflammation by displaying a more aggressive inflammatory path of macrophage activation syndrome (MAS), a rare and often deadly complication characterized by coagulopathy, cytopenia, and multiorgan dysfunction. The overlap of the diagnostic category with other inflammatory diseases interferes with timely intervention; however, the high mortality rate of the syndrome without intense immune suppression highlights the virulence of unrestrained immune stimulation [118–120]. Although immune hyperactivity is a defining feature in many severe patients, immune suppression is equally an important outcome of SARS-CoV-2 infection, and the disease has often been documented to cause extended lymphopenia in both T- and B-cells. Immunosuppression seems to be a result of direct viral toxicity, inhibition of the bone marrow by cytokines, and eventual immune fatigue. Low lymphocyte counts are always linked to increased morbidity, a high risk of complicated infections, and a decreased response to immunization [45,121,122].

Long COVID also sheds additional light on the quandary presented by immune exhaustion, the condition of upregulated inhibitory receptors on T cells and consequent non-clearance of viruses that precludes speedy recuperation. Similarly, dysregulated natural killer (NK) cell populations have been identified as a key factor in the failure to maintain the immune response in severe acute COVID-19. Loss of NK cell numbers and cytotoxicity allows unobstructed replication of the virus and precludes early immune control. Although efforts have been made to determine strategies that may boost NK cell activity, their use in serious stages of the disease remains speculative [123,124].

Systemic immune responses triggered by SARS-CoV-2 have gained prominence in the broader discussion of the pandemic. In addition to immediate causative inflammatory cascades that were known to occur, there is a significant autoimmune phenomenon that has now been observed. Viral mimicry of antigens on host tissues seems to be the cause of self-directed immune responses that take the form of Guillain-Barr syndrome, systemic lupus erythematosus flares, and numerous rheumatological complications. These

disorders may appear either in the acute phase of infection or in the later stage, requiring urgent immunosuppressive treatment to avoid irreversible tissue damage [41,125,126]. In parallel, antiviral antibody type and delayed or poorly produced deficits in immunocompromised patients, such as those with malignancies, organ transplants, or chronic administration of immunosuppressive drugs, exacerbate viral persistence in the host, increase susceptibility to reinfection, and decrease the effectiveness of vaccines. The need to implement individual and prophylactic measures and strict clinical supervision is evidenced by these situations [127,128].

Chronic immune dysregulation has also been redirected through long COVID. Even after recovery, many people still experience fatigue, musculoskeletal pain, and cognitive disturbances, which are often coupled with aberrant cytokine release, immune cell dysregulation, and the appearance of autoantibodies. This leaves an unfinished and non-linear map of immune recovery in post-acute COVID-19 without concluding the rudiments of immune restoration, as the exact mechanisms are not fully understood [129]. Along with this disturbance, we have also seen multisystem inflammatory syndromes that develop in both children (MIS-C) and adults (MIS-A) and may develop weeks after being infected. The conditions are similar to Kawasaki disease or toxic shock syndrome and include system-wide inflammation and dysfunction in the cardiac, renal, gastrointestinal, and skin systems. It has been shown that early diagnosis and the resulting prompt immunomodulation are central to alleviating morbidity and death [45,130].

Recent data have shown that SARS-CoV-2 affects the reproductive health of both sexes. Orchitis and low sperm quality have been reported in 19% of males, and viral RNA has been found in semen samples during acute infection. The average testosterone level fell by 30% during acute illness, and 25% of patients had not recovered in 3 months. Menstrual disorders, including changes in cycle duration, flow, and dysmenorrhea intensity, were observed in 28% of female patients. Pregnancy outcomes were associated with a higher risk of preterm birth (OR 1.7, 95% CI: 1.4–2.0) and preeclampsia (OR 1.6, 95% CI: 1.3–1.9) [130].

Approximately 20% of COVID-19 patients have cutaneous manifestations that exhibit various morphologies. Maculopapular eruptions (47% of skin manifestations) are usually present at disease onset. COVID toes (chilblain-like lesions) occurred in 19% of patients with skin involvement, mostly in younger patients. Other frequent patterns included urticarial eruptions (19%), vesicular eruptions (9%), and livedo/necrosis (6%). These symptoms are associated with disease severity, and livedo and necrosis are associated with higher mortality (OR 3.2, 95% CI: 2.1–4.8) [131].

COVID-19 affects the hematological system in more ways than just coagulopathy [131]. Approximately 83% of hospitalized patients have lymphopenia, and the depletion of CD4+ and CD8+ T-cells is associated with disease severity. Thrombocytopenia is present in 36% of severe cases, and thrombocytosis can occur during recovery. Hemophagocytic lymphohistiocytosis is rare (0.5%) and fatal (>50%). Antiphospholipid antibodies are found in 52% of critically ill patients and in immune thrombocytopenic purpura during the post-acute stages [130–133].

Taken together, these patterns suggest that SARS-CoV-2 causes a protracted dysregulation of the immune-endocrine axis, in addition to inducing an immune response. The simultaneous presence of inflammatory hyperactivity and immunological exhaustion makes the choice of clinical actions difficult and hinders patient recovery. Finding an optimal balance between augmenting viral clearance and moderating the effects of immune-induced injury has become the central dilemma in the clinical treatment of COVID-19 immunopathology, with implications that go far beyond the emergency illness phase.

9. Mental Health Consequences of COVID-19: A Syndemic of Psychological Disruption

The mental health sequel of the COVID-19 pandemic is a secondary pandemic in the truest meaning of the word and is already causing such disruptions in both adult and pediatric populations of all socioeconomic backgrounds and health statuses. A rapid increase in anxiety disorder cases was greatly driven by the constant threat of infection, economic downturn, and social isolation; such an upswing was especially significant in front-line workers, patients with previous psychological pathology, and representatives of minorities [132,133]. Depression was also sharpened, being aided by losses or the loss of work and the weakening of social support networks, which frequently presented themselves in the forms of widespread anhedonia, despair, and cognitive disruptions, becoming prevalent among the earlier-willing psychologically healthy people [134–136]. At the same time, post-traumatic stress disorder (PTSD) increased significantly on the part of not only survivors but also grieving families and medical providers who faced unending death, lack of critical resources, as well as multidimensional ethical judgment. Common and debilitating symptoms include flashbacks, dissociation, and intrusive memories, among others, which highlights the extreme need for trauma-informed care systems [137]. Another feature was insomnia and circadian disturbances, as stress and changes in lifestyle and screen use increased sleep disturbances, which sustained mood dysregulation and lowered resilience [138]. Such a phenomenon as the so-called brain fog (considered a permanent lack of cognitive efficiency, memory, and decency of thoughts) can be regarded as a particularly noticeable symptom in survivors. Although the etiology is still unclear, neuroinflammation, microvascular damage, and the neurotropism of the virus are deemed possible pathogenesis; in any case, these damage features, even in patients with mild initial disease, have a significant negative effect on everyday performance and the quality of life in the long term [139]. The introduced social isolation (particularly lockdowns) increased negative mood and social isolation, which led to mild cognitive decline, especially in the elderly and single individuals. Simultaneously, the use of substances intensified; alcohol, tobacco, and unprescribed drug consumption increased as maladaptive coping styles led to increased addiction levels and increased pressure on overburdened healthcare systems [140]. These combined psychosocial stressors also triggered an augmentation of suicidal thoughts and actions, especially among younger people and socioeconomically disadvantaged groups. Burnout has become a pandemic among healthcare workers, characterized by emotional fatigue, depersonalization, and lack of efficacy. This was the result of long working hours, constant interaction with death, and lack of support provided by institutions, all of which jeopardized the standards of patient care [141]. Moreover, hygiene consciousness and fear of infection associated with the pandemic became compulsive and obsessive in those who already had it or developed health anxiety and OCD, especially with the intensification and prolonged coverage by the media and unclear communication about health factors [142,143]. Overall, these results imply that COVID-19 was both a biological pathogen and a psychological stressor in the sense that it impaired not only emotional regulation and neurocognitive performance but also social connection. As a result, the response to the mental health fallout requires a combination of short-term psychological responses with systemic changes, rooted in the reform of all pandemic preparedness and recovery systems to incorporate mental healthcare support.

10. Impact of SARS-CoV-2 Variants on Symptom Variability

Although the current review investigates the organ-specific complications of COVID-19 in the wider context of clinical practice, it should be noted that symptom-reporting profiles and the involvement of specific organ systems differ among the various SARS-CoV-2 variants [144–146]. Specifically, the Delta variant was linked to severe respiratory involvement and hospitalization rates, whereas Omicron was characterized by the prevalence of upper airway symptoms and a relatively low rate of acute respiratory distress syndrome (ARDS) in vaccinated populations [147–152]. Variant-specific clinical manifestations are compared in Table 10.

Table 10. Variant-specific manifestation patterns.

Variant	Key Features	Organ Predilection	Severity
Alpha (B.1.1.7)	Original symptom profile	Respiratory predominant	High
Delta (B.1.617.2)	Severe respiratory involvement	Lower respiratory tract	Highest
Omicron (B.1.1.529)	Upper airway symptoms	Upper respiratory tract	Lower (vaccinated)
	Reduced anosmia/ageusia	Less neurotropic	Variable

Neurological effects, including anosmia and ageusia, which formerly abounded in earlier strains, have been reported to decrease in more recent strains [153,154]. These changing symptom patterns highlight the importance of variant-specific studies in the interpretation of post-acute sequelae and long COVID outcomes [155,156]. Nonetheless, essential pathological processes, including endothelial dysfunction and systemic inflammation, seem to be similar across variants, which explains why a systemic approach was taken in this review [157–161].

A summary of organ system involvement, including acute and long-term prevalence, key biomarkers, and severity associations, is provided in Table 11. The acute-phase distribution of organ system involvement is shown in Figure 5.

Table 11. Organ system involvement—frequency and key markers.

Organ System	Acute Phase (%)	Long-Term (6 mo) (%)	Key Biomarkers	Severity Association
Pulmonary	78	24	DLCO, CT findings	High
Cardiovascular	32	11	Troponin, NT-proBNP	High
Neurological	43	32	MRI changes, EEG	Moderate
Renal *	28	35	Creatinine, proteinuria	High
Hepatic	38	8	AST, ALT, bilirubin	Moderate
GI	24	16	Fecal calprotectin	Low–Moderate

* Renal involvement includes both acute kidney injury and chronic effects. Source: Current review synthesis of published data, 2020–2025.

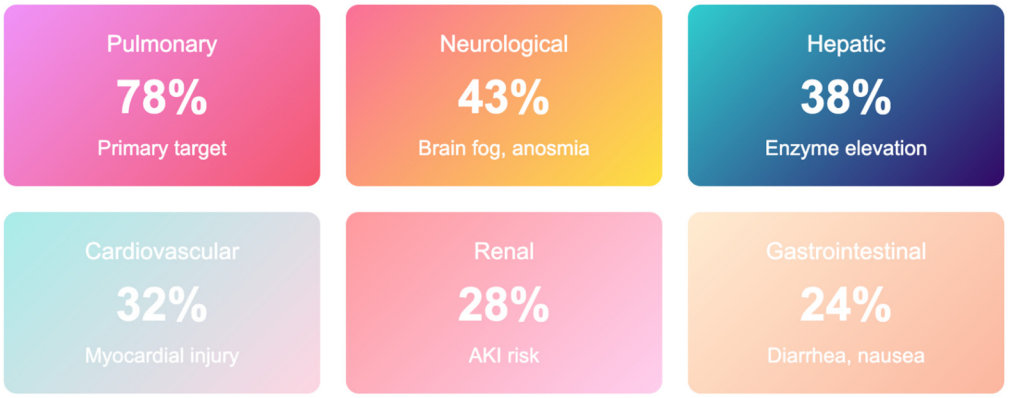

Figure 5. Prevalence of Multi-Organ System Involvement in Hospitalized COVID-19 Patients. Note: Percentage of hospitalized COVID-19 patients showing involvement of different organ systems based on a systematic review of 161 studies (n > 2 million patients). The data represent acute-phase manifestations.

11. Conclusions

This systematic narrative review of 161 peer-reviewed studies involving more than 2 million COVID-19 patients offers strong evidence that SARS-CoV-2 is a multi-system disease with interrelated and overlapping pathophysiological mechanisms. The quantitative synthesis showed that 78% of hospitalized patients had pulmonary organ involvement, 32% had cardiovascular involvement, 43% had neurological involvement, and 28% had renal involvement, with 10-35% having persistent organ dysfunction at 6 months post-infection. A comparison of acute involvement and persistent dysfunction at six months is shown in Figure 6**.** The different clinical manifestations are due to the shared mechanisms of cytokine storm (IL-6 > 100 pg/mL in 72% of severe cases), endothelial dysfunction (biomarkers elevated in 87% of patients), and microvascular thrombosis (D-dimer > 2000 ng/mL in 46% of patients). These results justify a paradigm shift towards integrated, multidisciplinary management of organ-specific management. Healthcare systems should be ready to implement long-term surveillance and rehabilitation programs, and research priorities should focus on the mechanistic understanding of the maintenance of organ dysfunction and how particular therapeutic interventions can be developed. The evidence, which is presented with moderate to high confidence of major organ systems, is a source of clinical guidelines and healthcare policies in the post-pandemic world.

Figure 6. Persistent organ dysfunction at 6 months post-infection. Note: Comparison of acute phase involvement versus persistent dysfunction 6 months post-COVID-19 infection across different organ systems. Data were synthesized from longitudinal cohort studies included in the systematic review.

The COVID-19 pandemic has revealed a much more complex pathophysiological picture than was initially expected. Although SARS-CoV-2 was originally considered a respiratory pathogen, with the current clinical, epidemiological, and radiographic evidence, it is now evident that its sequelae are much more far-reaching than pulmonary damage and do not spare practically any significant body system. The current review integrates peer-reviewed data published from 2020 to the end of 2025 to provide a coherent image of COVID-19 as a multisystemic illness with the utmost complexity of mechanisms that are partly shared: cytokine storm, ACE2-mediated viral infection, endothelium disruption, and thrombo-inflammation.

This review has been able to specifically respond to the piecemeal quality inherent in the current literature, as the majority of the available commentaries only comment on individual symptoms or the results of organ-specific testing. Its relative architecture and mechanism-oriented approach occupy a vital gap, shedding light on how and why COVID-19 causes lasting multi-organ complications, even among people who never went into the hospital or who showed only mild illness at the start. What makes it original is not only a cross-organ view but also a description of shared molecular and clinical pathways that can be used to shape both diagnosis and therapeutic practice.

This review also combines recent debates concerning SARS-CoV-2 variants and their possible impact on organ-specific sequelae, which have been poorly addressed in previous commentaries. Since it highlights the changing post-acute trends, this study emphasizes the importance of dynamic, long-range patient-monitoring systems that are capable of responding to the new variant patterns and new indicators of organ weakness.

In conclusion, this short review recontextualizes COVID-19 as a long-term, systemic condition that may involve interdisciplinary approaches to post-infection management, as well as long-term, system-wide, population-wide monitoring. Its value is in bringing together scattered pieces of evidence in a form that is both clinically useful and available to practice to inform clinicians, researchers, and policymakers. Hopefully, it will motivate more longitudinal studies and trigger the transition to the development of integrated care processes that could consider the variety and long-term effects of SARS-CoV-2 on human health.

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References

1. Perico, L.; Benigni, A.; Remuzzi, G. SARS-CoV-2 and the spike protein in endotheliopathy. *Trends Microbiol.* **2023**, *32*, 53–67. [CrossRef]
2. Pons, S.; Fodil, S.; Azoulay, E.; Zafrani, L. The vascular endothelium: The cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit. Care* **2020**, *24*, 353. [CrossRef]
3. Subramaniam, S.; Jose, A.; Kenney, D.; O'cOnnell, A.K.; Bosmann, M.; Douam, F.; Crossland, N. Challenging the notion of endothelial infection by SARS-CoV-2: Insights from the current scientific evidence. *Front. Immunol.* **2025**, *16*, 1443932. [CrossRef]

4. Parotto, M.; Gyöngyösi, M.; Howe, K.; Myatra, S.N.; Ranzani, O.; Shankar-Hari, M.; Herridge, M.S. Post-acute sequelae of COVID-19: Understanding and addressing the burden of multisystem manifestations. *Lancet Respir. Med.* **2023**, *11*, 739–754. [CrossRef]
5. Proal, A.D.; VanElzakker, M.B. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Front. Microbiol.* **2021**, *12*, 698169. [CrossRef] [PubMed]
6. Gusev, E.; Sarapultsev, A. Exploring the Pathophysiology of Long COVID: The Central Role of Low-Grade Inflammation and Multisystem Involvement. *Int. J. Mol. Sci.* **2024**, *25*, 6389. [CrossRef]
7. Sherif, Z.A.; Gomez, C.R.; Connors, T.J.; Henrich, T.J.; Reeves, W.B.; Force, R.M.P.T. Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC). *eLife* **2023**, *12*, e86002. [CrossRef]
8. Mehandru, S.; Merad, M. Pathological sequelae of long-haul COVID. *Nat. Immunol.* **2022**, *23*, 194–202. [CrossRef] [PubMed]
9. Castanares-Zapatero, D.; Chalon, P.; Kohn, L.; Dauvrin, M.; Detollenaere, J.; de Noordhout, C.M.; Jong, C.P.-D.; Cleemput, I.; Heede, K.V.D. Pathophysiology and mechanism of long COVID: A comprehensive review. *Ann. Med.* **2022**, *54*, 1473–1487. [CrossRef]
10. Golzardi, M.; Hromić-Jahjefendić, A.; Šutković, J.; Aydin, O.; Ünal-Aydın, P.; Bećirević, T.; Redwan, E.M.; Rubio-Casillas, A.; Uversky, V.N. The Aftermath of COVID-19: Exploring the Long-Term Effects on Organ Systems. *Biomedicines* **2024**, *12*, 913. [CrossRef] [PubMed]
11. Semo, D.; Shomanova, Z.; Sindermann, J.; Mohr, M.; Evers, G.; Motloch, L.J.; Reinecke, H.; Godfrey, R.; Pistulli, R. Persistent Monocytic Bioenergetic Impairment and Mitochondrial DNA Damage in PASC Patients with Cardiovascular Complications. *Int. J. Mol. Sci.* **2025**, *26*, 4562. [CrossRef] [PubMed]
12. Menezes, F.; Palmeira, J.D.F.; Oliveira, J.D.S.; Argañaraz, G.A.; Soares, C.R.J.; Nóbrega, O.T.; Ribeiro, B.M.; Argañaraz, E.R. Unraveling the SARS-CoV-2 spike protein long-term effect on neuro-PASC. *Front. Cell. Neurosci.* **2024**, *18*, 1481963. [CrossRef]
13. Ong, I.Z.; Kolson, D.L.; Schindler, M.K. Mechanisms, Effects, and Management of Neurological Complications of Post-Acute Sequelae of COVID-19 (NC-PASC). *Biomedicines* **2023**, *11*, 377. [CrossRef] [PubMed]
14. Smadja, D.M.; Mentzer, S.J.; Fontenay, M.; Laffan, M.A.; Ackermann, M.; Helms, J.; Jonigk, D.; Chocron, R.; Pier, G.B.; Gendron, N.; et al. COVID-19 is a systemic vascular hemopathy: Insight for mechanistic and clinical aspects. *Angiogenesis* **2021**, *24*, 755–788. [CrossRef]
15. Akhmerov, A.; Marbán, E. COVID-19 and the Heart. *Circ. Res.* **2020**, *126*, 1443–1455. [CrossRef] [PubMed]
16. Long, B.; Brady, W.J.; Koyfman, A.; Gottlieb, M. Cardiovascular complications in COVID-19. *Am. J. Emerg. Med.* **2020**, *38*, 1504–1507. [CrossRef]
17. Joshee, S.; Vatti, N.; Chang, C. Long-Term Effects of COVID-19. *Mayo Clin. Proc.* **2022**, *97*, 579–599. [CrossRef]
18. Ball, L.; Silva, P.L.; Giacobbe, D.R.; Bassetti, M.; Zubieta-Calleja, G.R.; Rocco, P.R.; Pelosi, P. Understanding the pathophysiology of typical acute respiratory distress syndrome and severe COVID-19. *Expert Rev. Respir. Med.* **2022**, *16*, 437–446. [CrossRef]
19. Gibson, P.G.; Qin, L.; Puah, S.H. COVID-19 acute respiratory distress syndrome (ARDS): Clinical features and differences from typical pre-COVID-19 ARDS. *Med. J. Aust.* **2020**, *213*, 54–56e1. [CrossRef]
20. Grasselli, G.; Tonetti, T.; Protti, A.; Langer, T.; Girardis, M.; Bellani, G.; Laffey, J.; Carrafiello, G.; Carsana, L.; Rizzuto, C.; et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: A multicentre prospective observational study. *Lancet Respir. Med.* **2020**, *8*, 1201–1208. [CrossRef] [PubMed]
21. Yu, J.; Zhang, K.; Chen, T.; Lin, R.; Chen, Q.; Chen, C.; Tong, M.; Chen, J.; Yu, J.; Lou, Y.; et al. Temporal patterns of organ dysfunction in COVID-19 patients hospitalized in the intensive care unit: A group-based multitrajectory modeling analysis. *Int. J. Infect. Dis.* **2024**, *144*, 107045. [CrossRef]
22. Bertilacchi, M.S.; Piccarducci, R.; Celi, A.; Germelli, L.; Romei, C.; Bartholmai, B.J.; Barbieri, G.; Giacomelli, C.; Martini, C. Blood oxygenation state in COVID-19 patients: Unexplored role of 2,3-bisphosphoglycerate. *Biomed. J.* **2024**, *47*, 100723. [CrossRef]
23. Gutowski, M.; Klimkiewicz, J.; Rustecki, B.; Michałowski, A.; Paryż, K.; Lubas, A. Effect of Respiratory Failure on Peripheral and Organ Perfusion Markers in Severe COVID-19: A Prospective Cohort Study. *J. Clin. Med.* **2024**, *13*, 469. [CrossRef] [PubMed]
24. Sudo, K.; Kinoshita, M.; Kawaguchi, K.; Kushimoto, K.; Yoshii, R.; Inoue, K.; Yamasaki, M.; Matsuyama, T.; Kooguchi, K.; Takashima, Y.; et al. Case study observational research: Inflammatory cytokines in the bronchial epithelial lining fluid of COVID-19 patients with acute hypoxemic respiratory failure. *Crit. Care* **2024**, *28*, 134. [CrossRef] [PubMed]
25. Williams, J.L.; Jacobs, H.M.; Lee, S. Pediatric Myocarditis. *Cardiol. Ther.* **2023**, *12*, 243–260. [CrossRef]
26. Amin, B.J.H.; Kakamad, F.H.; Ahmed, G.S.; Ahmed, S.F.; Abdulla, B.A.; Mohammed, S.H.; Mikael, T.M.; Salih, R.Q.; Ali, R.K.; Salh, A.M.; et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. *Ann. Med. Surg.* **2022**, *77*, 103590. [CrossRef] [PubMed]
27. Patton, M.J.; Benson, D.; Robison, S.W.; Raval, D.; Locy, M.L.; Patel, K.; Grumley, S.; Levitan, E.B.; Morris, P.; Might, M.; et al. Characteristics and determinants of pulmonary long COVID. *J. Clin. Investig.* **2024**, *9*, e177518. [CrossRef]
28. Duong-Quy, S.; Vo-Pham-Minh, T.; Tran-Xuan, Q.; Huynh-Anh, T.; Vo-Van, T.; Vu-Tran-Thien, Q.; Nguyen-Nhu, V. Post-COVID-19 Pulmonary Fibrosis: Facts—Challenges and Futures: A Narrative Review. *Pulm. Ther.* **2023**, *9*, 295–307. [CrossRef]

29. Malas, M.B.; Naazie, I.N.; Elsayed, N.; Mathlouthi, A.; Marmor, R.; Clary, B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine* **2020**, *29–30*, 100639. [CrossRef]
30. Lodigiani, C.; Iapichino, G.; Carenzo, L.; Cecconi, M.; Ferrazzi, P.; Sebastian, T.; Kucher, N.; Studt, J.-D.; Sacco, C.; Bertuzzi, A.; 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. [CrossRef]
31. Poor, H.D. Pulmonary Thrombosis and Thromboembolism in COVID-19. *Chest* **2021**, *160*, 1471–1480. [CrossRef]
32. Bonow, R.O.; Fonarow, G.C.; O'Gara, P.T.; Yancy, C.W. Association of Coronavirus Disease 2019 (COVID-19) with Myocardial Injury and Mortality. *JAMA Cardiol.* **2020**, *5*, 751–753. [CrossRef]
33. Deng, Q.; Hu, B.; Zhang, Y.; Wang, H.; Zhou, X.; Hu, W.; Cheng, Y.; Yan, J.; Ping, H.; Zhou, Q. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. *Int. J. Cardiol.* **2020**, *311*, 116–121. [CrossRef]
34. Lala, A.; Johnson, K.W.; Januzzi, J.L.; Russak, A.J.; Paranjpe, I.; Richter, F.; Zhao, S.; Somani, S.; Van Vleck, T.; Vaid, A.; et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. *JACC* **2020**, *76*, 533–546. [CrossRef]
35. Katsoularis, I.; Jerndal, H.; Kalucza, S.; Lindmark, K.; Fonseca-Rodríguez, O.; Connolly, A.-M.F.; Braunschweig, F. Risk of arrhythmias following COVID-19: Nationwide self-controlled case series and matched cohort study. *Eur. Heart J. Open* **2023**, *3*, oead120. [CrossRef] [PubMed]
36. Shakir, M.; Hassan, S.M.; Adil, U.; Abidi, S.M.A.; Ali, S.A.; Yaqoob, U. Unveiling the silent threat of new onset atrial fibrillation in covid-19 hospitalized patients: A retrospective cohort study. *PLoS ONE* **2024**, *19*, e0291829. [CrossRef]
37. Saha, S.A.; Russo, A.M.; Chung, M.K.; Deering, T.F.; Lakkireddy, D.; Gopinathannair, R. COVID-19 and Cardiac Arrhythmias: A Contemporary Review. *Curr. Treat. Options Cardiovasc. Med.* **2022**, *24*, 87–107. [CrossRef] [PubMed]
38. Delorey, T.M.; Ziegler, C.G.K.; Heimberg, G.; Normand, R.; Yang, Y.; Segerstolpe, Å.; Abbondanza, D.; Fleming, S.J.; Subramanian, A.; Montoro, D.T.; et al. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature* **2021**, *595*, 107–113. [CrossRef] [PubMed]
39. Bonaventura, A.; Vecchié, A.; Dagna, L.; Martinod, K.; Dixon, D.L.; Van Tassell, B.W.; Dentali, F.; Montecucco, F.; Massberg, S.; Levi, M.; et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat. Rev. Immunol.* **2021**, *21*, 319–329. [CrossRef]
40. Alanazi, T.K.A.; Alahmari, N.F.A.; Qubays, F.E.I.; Alenezi, S.H.I.; Alenezi, M.F.M. Post COVID-19 Organizing Pneumonia: A Systematic Review and Meta-analysis. *J. Pharm. Res. Int.* **2021**, *33*, 259–270. [CrossRef]
41. Zhou, C. The Impact of COVID-19 on Different Human Systems and Related Research Progress. *Highlights Sci. Eng. Technol.* **2024**, *91*, 145–150. [CrossRef]
42. Gerayeli, F.V.; Park, H.Y.; Milne, S.; Li, X.; Yang, C.X.; Tuong, J.; Eddy, R.L.; Vahedi, S.M.; Guinto, E.; Cheung, C.Y.; et al. Single-cell sequencing reveals cellular landscape alterations in the airway mucosa of patients with pulmonary long COVID. *Eur. Respir. J.* **2024**, *64*, 2301947. [CrossRef]
43. Low, R.N.; Low, R.J.; Akrami, A. A review of cytokine-based pathophysiology of Long COVID symptoms. *Front. Med.* **2023**, *10*, 1011936. [CrossRef]
44. Alabdali, A.Y.M.; Chinnappan, S.; Basma, M.; Mogana, R.; Khalivulla, S.I.; Rahman, H. Impact of COVID-19 on Multiple Body Organ Failure: A Review. *Int. J. Appl. Pharm.* **2021**, *13*, 54–59. [CrossRef]
45. Shi, H.; Xu, J. The impact of COVID-19 on human body. *Highlights Sci. Eng. Technol.* **2023**, *36*, 1186–1192. [CrossRef]
46. Sozzi, F.B.; Gherbesi, E.; Faggiano, A.; Gnan, E.; Maruccio, A.; Schiavone, M.; Iacuzio, L.; Carugo, S. Viral Myocarditis: Classification, Diagnosis, and Clinical Implications. *Front. Cardiovasc. Med.* **2022**, *9*, 908663. [CrossRef]
47. Yan, P.; Yang, S.; Wang, T. Management Status of Myocarditis-Related Sudden Cardiac Death. *Rev. Cardiovasc. Med.* **2024**, *25*, 452. [CrossRef] [PubMed]
48. Rekalova, E. Long-term Consequences of COVID-19 (Review). *Int. J. Rehabil. Palliat. Med.* **2023**, *1*, 100–104. [CrossRef]
49. Mroueh, A.; Fakih, W.; Carmona, A.; Trimaille, A.; Matsushita, K.; Marchandot, B.; Qureshi, A.W.; Gong, D.-S.; Auger, C.; Sattler, L.; et al. COVID-19 promotes endothelial dysfunction and thrombogenicity: Role of proinflammatory cytokines/SGLT2 prooxidant pathway. *J. Thromb. Haemost.* **2023**, *22*, 286–299. [CrossRef]
50. Peng, X.; Wang, Y.; Xi, X.; Jia, Y.; Tian, J.; Yu, B.; Tian, J. Promising Therapy for Heart Failure in Patients with Severe COVID-19: Calming the Cytokine Storm. *Cardiovasc. Drugs Ther.* **2021**, *35*, 231–247. [CrossRef]
51. Nguyen, A.; Corcoran, J.; Nedzlek, C.D. Sinus Arrest in Asymptomatic COVID-19 Infection. *Cureus* **2022**, *14*, e23736. [CrossRef]
52. Kar, M. Vascular Dysfunction and Its Cardiovascular Consequences During and After COVID-19 Infection: A Narrative Review. *Vasc. Health Risk Manag.* **2022**, *18*, 105–112. [CrossRef]
53. Chen, H.; Peng, J.; Wang, T.; Wen, J.; Chen, S.; Huang, Y.; Zhang, Y. Counter-regulatory renin-angiotensin system in hypertension: Review and update in the era of COVID-19 pandemic. *Biochem. Pharmacol.* **2022**, *208*, 115370. [CrossRef]

54. Hărșan, S.T.; Sin, A.I. The Involvement and Manifestations of SARS-CoV-2 Virus in Cardiovascular Pathology. *Medicina* **2025**, *61*, 773. [CrossRef] [PubMed]
55. de Oliveira, E.F.B.; Varela, J.P.D.V.; Liphaus, L.A.; Rosado, Á.B.; Nobre, J.M.; Brambilla, B.A.; Barbosa, A.L.F.; Preti, L.C.; Figueiredo, B.D.O.; Moutinho, B.D.F.; et al. Takotsubo Cardiomyopathy and the Heart-Brain Axis. *Health Soc.* **2025**, *5*, 69–78. [CrossRef]
56. Al Houri, H.N.; Jomaa, S.; Jabra, M.; Alhouri, A.N.; Latifeh, Y. Pathophysiology of stress cardiomyopathy: A comprehensive literature review. *Ann. Med. Surg.* **2022**, *82*, 104671. [CrossRef]
57. McMaster, M.W.D.; Dey, S.D.; Fishkin, T.; Wang, A.; Frishman, W.H.; Aronow, W.S. The Impact of Long COVID-19 on the Cardiovascular System. *Cardiol. Rev.* **2024**. [CrossRef]
58. Marques, K.C.; Quaresma, J.A.S.; Falcão, L.F.M. Cardiovascular autonomic dysfunction in "Long COVID": Pathophysiology, heart rate variability, and inflammatory markers. *Front. Cardiovasc. Med.* **2023**, *10*, 1256512. [CrossRef]
59. Hess, D.C.; Eldahshan, W.; Rutkowski, E. COVID-19-Related Stroke. *Transl. Stroke Res.* **2020**, *11*, 322–325. [CrossRef]
60. Beyerstedt, S.; Casaro, E.B.; Rangel, É.B. COVID-19: Angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur. J. Clin. Microbiol. Infect. Dis.* **2021**, *40*, 905–919. [CrossRef] [PubMed]
61. Ni, W.; Yang, X.; Yang, D.; Bao, J.; Li, R.; Xiao, Y.; Hou, C.; Wang, H.; Liu, J.; Yang, D.; et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit. Care* **2020**, *24*, 422. [CrossRef]
62. Shao, S.-C.; Lai, C.-C.; Chen, Y.-H.; Chen, Y.-C.; Hung, M.-J.; Liao, S.-C. Prevalence, incidence and mortality of delirium in patients with COVID-19: A systematic review and meta-analysis. *Age Ageing* **2021**, *50*, 1445–1453. [CrossRef]
63. Klopfenstein, T.; Kadiane-Oussou, N.; Toko, L.; Royer, P.-Y.; Lepiller, Q.; Gendrin, V.; Zayet, S. Features of anosmia in COVID-19. *Med. Mal. Infect.* **2020**, *50*, 436–439. [CrossRef]
64. Salih, R.; Hassan, R.; Ibrahim, S.N.; Omer, H.; Abdelsamad, A.; Elmustafa, F.; Elomeiri, L.; Mahmoud, S.; Ahmed, M.; Alsamani, R.H.; et al. The Neuro-cognitive Implications of COVID-19 Infection: A Systematic Review with an Insight into the Pathophysiology (P11-13.009). *Neurology* **2024**, *102* (Suppl. 1), 6303. [CrossRef]
65. Bommarito, G.; Garibotto, V.; Frisoni, G.B.; Assal, F.; Lalive, P.H.; Allali, G. The Two-Way Route between Delirium Disorder and Dementia: Insights from COVID-19. *Neurodegener. Dis.* **2022**, *22*, 91–103. [CrossRef]
66. Otani, K.; Fukushima, H.; Matsuishi, K. COVID-19 delirium and encephalopathy: Pathophysiology assumed in the first 3 years of the ongoing pandemic. *Brain Disord.* **2023**, *10*, 100074. [CrossRef]
67. Asadi-Pooya, A.A.; Akbari, A.; Emami, A.; Lotfi, M.; Rostamihosseinkhani, M.; Nemati, H.; Barzegar, Z.; Kabiri, M.; Zeraatpisheh, Z.; Farjoud-Kouhanjani, M.; et al. Long COVID syndrome-associated Brain Fog. *J. Med. Virol.* **2021**, *94*, 979–984. [CrossRef]
68. Córdova-Martínez, A.; Caballero-García, A.; Pérez-Valdecantos, D.; Roche, E.; Noriega-González, D.C. Peripheral Neuropathies Derived from COVID-19: New Perspectives for Treatment. *Biomedicines* **2022**, *10*, 1051. [CrossRef]
69. Islam, A.; Cavestro, C.; Alam, S.S.; Kundu, S.; Kamal, M.A.; Reza, F. Encephalitis in Patients with COVID-19: A Systematic Evidence-Based Analysis. *Cells* **2022**, *11*, 2575. [CrossRef]
70. Badenoch, J.B.; Rengasamy, E.R.; Watson, C.; Jansen, K.; Chakraborty, S.; Sundaram, R.D.; Hafeez, D.; Burchill, E.; Saini, A.; Thomas, L.; et al. Persistent neuropsychiatric symptoms after COVID-19: A systematic review and meta-analysis. *Brain Commun.* **2021**, *4*, fcab297. [CrossRef]
71. Quan, L.; Lu, W.; Zhen, R.; Zhou, X. Post-traumatic stress disorders, anxiety, and depression in college students during the COVID-19 pandemic: A cross-sectional study. *BMC Psychiatry* **2023**, *23*, 228. [CrossRef]
72. Xiong, J.; Lipsitz, O.; Nasri, F.; Lui, L.M.W.; Gill, H.; Phan, L.; Chen-Li, D.; Iacobucci, M.; Ho, R.; Majeed, A.; et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J. Affect. Disord.* **2020**, *277*, 55–64. [CrossRef]
73. Legrand, M.; Bell, S.; Forni, L.; Joannidis, M.; Koyner, J.L.; Liu, K.; Cantaluppi, V. Pathophysiology of COVID-19-associated acute kidney injury. *Nat. Rev. Nephrol.* **2021**, *17*, 751–764. [CrossRef]
74. Sharma, P.; Ng, J.H.; Bijol, V.; Jhaveri, K.D.; Wanchoo, R. Pathology of COVID-19-associated acute kidney injury. *Clin. Kidney J.* **2021**, *14*, i30–i39. [CrossRef]
75. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary manifestations of COVID-19. *Nat. Med.* **2020**, *26*, 1017–1032. [CrossRef]
76. Pei, G.; Zhang, Z.; Peng, J.; Liu, L.; Zhang, C.; Yu, C.; Ma, Z.; Huang, Y.; Liu, W.; Yao, Y.; et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *J. Am. Soc. Nephrol.* **2020**, *31*, 1157–1165. [CrossRef]
77. Tiwari, N.R.; Phatak, S.; Sharma, V.R.; Agarwal, S.K. COVID-19 and thrombotic microangiopathies. *Thromb. Res.* **2021**, *202*, 191–198. [CrossRef]
78. Bhaskar, S.; Sinha, A.; Banach, M.; Mittoo, S.; Weissert, R.; Kass, J.S.; Rajagopal, S.; Pai, A.R.; Kutty, S. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Front. Immunol.* **2020**, *11*, 1648. [CrossRef]

79. Genest, D.S.; Patriquin, C.J.; Licht, C.; John, R.; Reich, H.N. Renal Thrombotic Microangiopathy: A Review. *Am. J. Kidney Dis.* **2022**, *81*, 591–605. [CrossRef]
80. Vaira, L.A.; Salzano, G.; Deiana, G.; De Riu, G. In Response to Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope* **2020**, *130*, E695. [CrossRef]
81. Jdiaa, S.S.; Mansour, R.; El Alayli, A.; Gautam, A.; Thomas, P.; Mustafa, R.A. COVID–19 and Chronic Kidney Disease: An Updated Overview of Reviews. *J. Nephrol.* **2022**, *35*, 69–85. [CrossRef]
82. Shariff, S.; Uwishema, O.; Mizero, J.; Thambi, V.D.; Nazir, A.; Mahmoud, A.; Kaushik, I.; Khayat, S.; Maigoro, A.Y.; Awde, S.; et al. Long-term Cognitive Dysfunction After the COVID-19 Pandemic: A Narrative Review. *Ann. Med. Surg.* **2023**, *85*, 5504–5510. [CrossRef]
83. Cheng, Y.; Luo, R.; Wang, K.; Zhang, M.; Wang, Z.; Dong, L.; Li, J.; Yao, Y.; Ge, S.; Xu, G. Kidney Disease Is Associated with In-hospital Death of Patients with COVID-19. *Kidney Int.* **2020**, *97*, 829–838. [CrossRef]
84. Wang, Y.; Liu, S.; Liu, H.; Li, W.; Lin, F.; Jiang, L.; Li, X.; Xu, P.; Zhang, L.; Zhao, L.; et al. SARS-CoV-2 Infection of the Liver Directly Contributes to Hepatic Impairment in Patients with COVID-19. *J. Hepatol.* **2020**, *73*, 807–816. [CrossRef]
85. Sharma, A.; Jaiswal, P.; Kerakhan, Y.; Saravanan, L.; Murtaza, Z.; Zergham, A.; Honganur, N.-S.; Akbar, A.; Deol, A.; Francis, B.; et al. Liver Disease and Outcomes Among COVID-19 Hospitalized Patients—A Systematic Review and Meta-Analysis. *Ann. Hepatol.* **2021**, *21*, 100273. [CrossRef]
86. Bertolini, A.; Van De Peppel, I.P.; Bodewes, F.A.; Moshage, H.; Fantin, A.; Farinati, F.; Fiorotto, R.; Jonker, J.W.; Strazzabosco, M.; Verkade, H.J.; et al. Abnormal Liver Function Tests in Patients with COVID-19: Relevance and Potential Pathogenesis. *Hepatology* **2020**, *72*, 1864–1872. [CrossRef]
87. Kameswari, S.; Lakshmi, T.; Ezhilarasan, D. Impact of COVID 19 in Liver Disease Patients. *Int. J. Res. Pharm. Sci.* **2020**, *11*, 701–704. [CrossRef]
88. Yoo, H.W.; Jin, H.Y.; Yon, D.K.; Effenberger, M.; Shin, Y.H.; Kim, S.Y.; Yang, J.M.; Kim, M.S.; Koyanagi, A.; Jacob, L.; et al. Non-alcoholic Fatty Liver Disease and COVID-19 Susceptibility and Outcomes: A Korean Nationwide Cohort. *J. Korean Med. Sci.* **2021**, *36*, e291. [CrossRef]
89. Kurniawan, A.; Hariyanto, T.I. Non-alcoholic Fatty Liver Disease (NAFLD) and COVID-19 Outcomes: A Systematic Review, Meta-analysis and Meta-regression. *Narra J.* **2023**, *3*, e102. [CrossRef]
90. Singh, A.; Hussain, S.; Antony, B. Non-alcoholic Fatty Liver Disease and Clinical Outcomes in Patients with COVID-19: A Comprehensive Systematic Review and Meta-analysis. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 813–822. [CrossRef]
91. Huang, H.; Li, H.; Chen, S.; Zhou, X.; Dai, X.; Wu, J.; Zhang, J.; Shao, L.; Yan, R.; Wang, M.; et al. Prevalence and Characteristics of Hypoxic Hepatitis in COVID-19 Patients in the Intensive Care Unit: A First Retrospective Study. *Front. Med.* **2021**, *7*, 607206. [CrossRef]
92. Delgado, A.; Stewart, S.; Urroz, M.; Rodríguez, A.; Borobia, A.M.; Akatbach-Bousaid, I.; González-Muñoz, M.; Ramírez, E. Characterisation of Drug-Induced Liver Injury in Patients with COVID-19 Detected by a Proactive Pharmacovigilance Program from Laboratory Signals. *J. Clin. Med.* **2021**, *10*, 4432. [CrossRef]
93. Taneva, G.; Dimitrov, D.; Velikova, T. Liver Dysfunction as a Cytokine Storm Manifestation and Prognostic Factor for Severe COVID-19. *World J. Hepatol.* **2021**, *13*, 2005–2012. [CrossRef]
94. Fara, A.; Mitrev, Z.; Rosalia, R.A.; Assas, B.M. Cytokine Storm and COVID-19: A Chronicle of Pro-Inflammatory Cytokines. *Open Biol.* **2020**, *10*, 200160. [CrossRef]
95. Taquet, M.; Husain, M.; Geddes, J.R.; Luciano, S.; Harrison, P.J. Cerebral Venous Thrombosis and Portal Vein Thrombosis: A Retrospective Cohort Study of 537,913 COVID-19 Cases. *EClinicalMedicine* **2021**, *39*, 101061. [CrossRef]
96. El Hajra, I.; Llop, E.; Blanco, S.; Perelló, C.; Fernández-Carrillo, C.; Calleja, J.L. Portal Vein Thrombosis in COVID-19: An Underdiagnosed Disease? *J. Clin. Med.* **2024**, *13*, 5599. [CrossRef]
97. Gilani, M.; Akcan, T.; Patel, H.; Zahid, A. S3842 Acute Portal Vein Thrombosis in COVID-19 Patient: A Rare Thromboembolic Complication. *Am. J. Gastroenterol.* **2023**, *118*, S2461. [CrossRef]
98. Lebbe, A.; Aboulwafa, A.; Bayraktar, N.; Mushannen, B.; Ayoub, S.; Sarker, S.; Abdalla, M.N.; Mohammed, I.; Mushannen, M.; Yagan, L.; et al. New Onset of Acute and Chronic Hepatic Diseases Post-COVID-19 Infection: A Systematic Review. *Biomedicines* **2024**, *12*, 2065. [CrossRef] [PubMed]
99. Stasi, C. Post-COVID-19 Pandemic Sequelae in Liver Diseases. *Life* **2025**, *15*, 403. [CrossRef]
100. D'aMico, F.; Baumgart, D.C.; Danese, S.; Peyrin-Biroulet, L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 1663–1672. [CrossRef]
101. Shchikota, A.; Pogonchenkova, I.; Turova, E.; Starodubova, A.; Nosova, N. COVID-19-associated diarrhea. *Probl. Nutr.* **2021**, *90*, 18–30. [CrossRef]
102. Wang, F.; Zheng, S.; Zheng, C.; Sun, X. Attaching Clinical Significance to COVID-19-associated diarrhea. *Life Sci.* **2020**, *260*, 118312. [CrossRef]

103. Andrews, P.L.; Cai, W.; A Rudd, J.; Sanger, G.J. COVID-19, Nausea, and Vomiting. *J. Gastroenterol. Hepatol.* **2020**, *36*, 646–656. [CrossRef]
104. Ng, S.C.; Tilg, H. COVID-19 and the Gastrointestinal Tract: More Than Meets the Eye. *Gut* **2020**, *69*, 973–974. [CrossRef]
105. Kumar, V.C.S.; Mukherjee, S.; Harne, P.S.; Subedi, A.; Ganapathy, M.K.; Patthipati, V.S.; Sapkota, B. Novelty in the Gut: A Systematic Review and Meta-analysis of the Gastrointestinal Manifestations of COVID-19. *BMJ Open Gastroenterol.* **2020**, *7*, e000417. [CrossRef] [PubMed]
106. Pokharel, A.; Acharya, I.; Chaudhary, R.K.; Songmen, S.; Williams, R. Superior Mesenteric Artery Thrombosis and Intestinal Ischemia as a Consequence of COVID-19 Infection. *Cureus* **2023**, *15*, e37259. [CrossRef]
107. Hayashi, Y.; Wagatsuma, K.; Nojima, M.; Yamakawa, T.; Ichimiya, T.; Yokoyama, Y.; Kazama, T.; Hirayama, D.; Nakase, H. The Characteristics of Gastrointestinal Symptoms in Patients with Severe COVID-19: A Systematic Review and Meta-analysis. *J. Gastroenterol.* **2021**, *56*, 409–420. [CrossRef] [PubMed]
108. Balaphas, A.; Gkoufa, K.; Colucci, N.; Perdikis, K.-C.; Gaudet-Blavignac, C.; Pataky, Z.; Carballo, S.; Ris, F.; Stirnemann, J.; Lovis, C.; et al. Abdominal Pain Patterns During COVID-19: An Observational Study. *Sci. Rep.* **2022**, *12*, 14677. [CrossRef] [PubMed]
109. Haripersad, Y.V.; Kannegiesser-Bailey, M.; Morton, K.; Skeldon, S.; Shipton, N.; Edwards, K.; Newton, R.; Newell, A.; Stevenson, P.G.; Martin, A.C. Outbreak of Anorexia Nervosa Admissions During the COVID-19 Pandemic. *Arch. Dis. Child.* **2021**, *106*, e15. [CrossRef]
110. Gilsbach, S.; Plana, M.T.; Castro-Fornieles, J.; Gatta, M.; Karlsson, G.P.; Flamarique, I.; Raynaud, J.-P.; Riva, A.; Solberg, A.-L.; van Elburg, A.A.; et al. Increase in Admission Rates and Symptom Severity of Childhood and Adolescent Anorexia Nervosa in Europe During the COVID-19 Pandemic: Data From Specialized Eating Disorder Units in Different European Countries. *Child Adolesc. Psychiatry Ment. Health* **2022**, *16*, 46. [CrossRef]
111. Mohamed, M.; Nassar, M.; Nso, N.; Alfishawy, M. Massive Gastrointestinal Bleeding in a Patient with COVID-19. *Arab. J. Gastroenterol.* **2021**, *22*, 177–179. [CrossRef]
112. Rathore, S.S.; Wint, Z.S.; Goyal, A.; Jeswani, B.M.; Farrukh, A.M.; Nieto-Salazar, M.A.; Thugu, T.R.; Erva, S.; Mehmood, R.; Toro-Velandia, A.C.; et al. Prevalence and Outcomes of Upper Gastrointestinal Bleeding in COVID-19: A Systematic Review and Meta-analysis. *Rev. Med. Virol.* **2024**, *34*, e2509. [CrossRef]
113. Chen, J.; Vitetta, L. The Gut–liver Axis in Chronic Liver Disease Associated with Severe COVID-19. *Eur. J. Gastroenterol. Hepatol.* **2021**, *33*, e1103. [CrossRef]
114. Cardinale, V.; Capurso, G.; Ianiro, G.; Gasbarrini, A.; Arcidiacono, P.G.; Alvaro, D. Intestinal Permeability Changes with Bacterial Translocation as Key Events Modulating Systemic Host Immune Response to SARS-CoV-2: A Working Hypothesis. *Dig. Liver Dis.* **2020**, *52*, 1383–1389. [CrossRef] [PubMed]
115. Batista, K.S.; de Albuquerque, J.G.; de Vasconcelos, M.H.A.; Bezerra, M.L.R.; Barbalho, M.B.d.S.; Pinheiro, R.O.; Aquino, J.d.S. Probiotics and Prebiotics: Potential Prevention and Therapeutic Target for Nutritional Management of COVID-19? *Nutr. Res. Rev.* **2021**, *36*, 181–198. [CrossRef]
116. Hiti, L.; Markovič, T.; Lainscak, M.; Lainščak, J.F.; Pal, E.; Mlinarič-Raščan, I. The immunopathogenesis of a cytokine storm: The key mechanisms underlying severe COVID-19. *Cytokine Growth Factor Rev.* **2025**, *82*, 1–17. [CrossRef] [PubMed]
117. Diamond, M.S.; Kanneganti, T.-D. Innate immunity: The first line of defense against SARS-CoV-2. *Nat. Immunol.* **2022**, *23*, 165–176. [CrossRef]
118. Ombrello, M.J.; Schulert, G.S. COVID-19 and Cytokine Storm Syndrome: Are There Lessons From Macrophage Activation Syndrome? *Transl. Res.* **2021**, *232*, 1–12. [CrossRef]
119. Chen, Y.; Shi, C.; Zhan, H.; Yang, B.B.; Liu, J.B.; Rong, P.; Luo, Y.; Yang, J. Drug-induced Liver Injury in COVID-19 Patients During Hospitalization. *Medicine* **2023**, *102*, e33294. [CrossRef] [PubMed]
120. Merad, M.; Martin, J.C. Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. *Nat. Rev. Immunol.* **2020**, *20*, 355–362. [CrossRef]
121. Popescu, I.; Snyder, M.E.; Iasella, C.J.; Hannan, S.J.; Koshy, R.; Burke, R.; Das, A.; Brown, M.J.; Lyons, E.J.; Lieber, S.C.; et al. $CD4^{+}$T-Cell Dysfunction in Severe COVID-19 Disease Is Tumor Necrosis Factor-α/Tumor Necrosis Factor Receptor 1–Dependent. *Am. J. Respir. Crit. Care Med.* **2022**, *205*, 1403–1418. [CrossRef]
122. Paules, C.I.; Nordwall, J.A.; Shaw-Saliba, K.; Aberg, J.A.; Gardner, E.M.; Goodman, A.L.; Kumarasamy, N.; Vasudeva, S.; Vock, D.M.; North, C.M.; et al. Blood absolute lymphocyte count and trajectory are important in understanding severe COVID-19. *BMC Infect. Dis.* **2025**, *25*, 67. [CrossRef]
123. Eaton-Fitch, N.; Rudd, P.; Er, T.; Hool, L.; Herrero, L.; Marshall-Gradisnik, S. Immune exhaustion in ME/CFS and long COVID. *J. Clin. Investig.* **2024**, *9*, e183810. [CrossRef]
124. Gil, A.; Hoag, G.E.; Salerno, J.P.; Hornig, M.; Klimas, N.; Selin, L.K. Identification of CD8 T-cell dysfunction associated with symptoms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID and treatment with a nebulized antioxidant/anti-pathogen agent in a retrospective case series. *Brain Behav. Immun. Health* **2023**, *36*, 100720. [CrossRef]

125. Rojas, M.; Herrán, M.; Ramírez-Santana, C.; Leung, P.S.; Anaya, J.-M.; Ridgway, W.M.; Gershwin, M.E. Molecular mimicry and autoimmunity in the time of COVID-19. *J. Autoimmun.* **2023**, *139*, 103070. [CrossRef]
126. Sundaresan, B.; Shirafkan, F.; Ripperger, K.; Rattay, K. The Role of Viral Infections in the Onset of Autoimmune Diseases. *Viruses* **2023**, *15*, 782. [CrossRef]
127. Pavia, G.; Quirino, A.; Marascio, N.; Veneziano, C.; Longhini, F.; Bruni, A.; Garofalo, E.; Pantanella, M.; Manno, M.; Gigliotti, S.; et al. Persistence of SARS-CoV-2 infection and viral *intra*- and *inter*-host evolution in COVID-19 hospitalized patients. *J. Med. Virol.* **2024**, *96*, e29708. [CrossRef] [PubMed]
128. Laracy, J.C.; Kamboj, M.; Vardhana, S.A. Long and persistent COVID-19 in patients with hematologic malignancies: From bench to bedside. *Curr. Opin. Infect. Dis.* **2022**, *35*, 271–279. [CrossRef] [PubMed]
129. Tsao, T.; Buck, A.M.; Grimbert, L.; LaFranchi, B.H.; Poblano, B.A.; Fehrman, E.A.; Dalhuisen, T.; Hsue, P.Y.; Kelly, J.D.; Martin, J.N.; et al. Long COVID Is Associated with Lower Percentages of Mature, Cytotoxic NK Cell Phenotypes. *J. Clin. Investig.* **2024**, *135*, e188182. [CrossRef] [PubMed]
130. Feldstein, L.R.; Tenforde, M.W.; Friedman, K.G.; Newhams, M.; Rose, E.B.; Dapul, H.; Soma, V.L.; Maddux, A.B.; Mourani, P.M.; Bowens, C.; et al. Characteristics and Outcomes of US Children and Adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) Compared with Severe Acute COVID-19. *JAMA* **2021**, *325*, 1074–1087. [CrossRef]
131. Ashonibare, V.J.; Ashonibare, P.J.; Akhigbe, T.M.; Akhigbe, R.E.; Schlatt, S. SARS-CoV-2 impairs male fertility by targeting semen quality and testosterone level: A systematic review and meta-analysis. *PLoS ONE* **2024**, *19*, e0307396. [CrossRef]
132. Delpino, F.M.; da Silva, C.N.; Jerônimo, J.S.; Mulling, E.S.; da Cunha, L.L.; Weymar, M.K.; Alt, R.; Caputo, E.L.; Feter, N. Prevalence of Anxiety During the COVID-19 Pandemic: A Systematic Review and Meta-analysis of Over 2 Million People. *J. Affect. Disord.* **2022**, *318*, 272–282. [CrossRef]
133. de Figueiredo, C.S.; Sandre, P.C.; Portugal, L.C.L.; Mázala-De-Oliveira, T.; da Silva Chagas, L.; Raony, Í.; Ferreira, E.S.; Giestal-De-Araujo, E.; dos Santos, A.A.; Bomfim, P.O.-S. COVID-19 pandemic impact on children and adolescents' mental health: Biological, environmental, and social factors. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2020**, *106*, 110171. [CrossRef] [PubMed]
134. Egbert, A.; Karpiak, S.; Havlik, R.; Cankurtaran, S.; Ozturk, S. Global Rise of Depression Prevalence Amid the COVID-19 Pandemic. *Innov. Aging* **2021**, *5* (Suppl. 1), 407. [CrossRef]
135. Ettman, C.K.; Abdalla, S.M.; Cohen, G.H.; Sampson, L.; Vivier, P.M.; Galea, S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. *JAMA Netw. Open* **2020**, *3*, e2019686. [CrossRef]
136. Zhu, C.; Zhang, T.; Li, Q.; Chen, X.; Wang, K. Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment. *Neurosci. Bull.* **2022**, *39*, 675–684. [CrossRef] [PubMed]
137. Huang, L.; Xu, X.; Zhang, L.; Zheng, D.; Liu, Y.; Feng, B.; Hu, J.; Lin, Q.; Xi, X.; Wang, Q.; et al. Post-traumatic Stress Disorder Symptoms and Quality of Life of COVID-19 Survivors at 6-Month Follow-Up: A Cross-Sectional Observational Study. *Front. Psychiatry* **2022**, *12*, 782478. [CrossRef]
138. Professor, M.A.; Rani, K.; Kalra, T.; Academician from Kurukshetra University Kurukshetra; Rani, M. Impact of COVID-19 on mind, body and soul. *Int. J. Adv. Res.* **2020**, *8*, 386–394. [CrossRef]
139. Cheng, Y.-H.; Tsai, M.-J.; Lu, Y.-J.; Fuh, J.-L. The Neuropsychological Impacts of COVID-19 in Non-hospitalized Patients with Long COVID and Brain Fog. *J. Chin. Med. Assoc.* **2024**, *88*, 58–64. [CrossRef]
140. Mallet, J.; Dubertret, C.; Le Strat, Y. Addictions in the COVID-19 Era: Current Evidence, Future Perspectives a Comprehensive Review. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2021**, *106*, 110070. [CrossRef]
141. Denning, M.; Goh, E.T.; Tan, B.; Kanneganti, A.; Almonte, M.; Scott, A.; Martin, G.; Clarke, J.; Sounderajah, V.; Markar, S.; et al. Determinants of Burnout and Other Aspects of Psychological Well-being in Healthcare Workers During the Covid-19 Pandemic: A Multinational Cross-sectional Study. *PLoS ONE* **2021**, *16*, e0238666. [CrossRef]
142. Ojalehto, H.J.; Abramowitz, J.S.; Hellberg, S.N.; Butcher, M.W.; Buchholz, J.L. Predicting COVID-19-related Anxiety: The Role of Obsessive-compulsive Symptom Dimensions, Anxiety Sensitivity and Body Vigilance. *J. Anxiety Disord.* **2021**, *83*, 102460. [CrossRef] [PubMed]
143. Ooi, L.L.; Liu, L.; Roberts, K.C.; Gariépy, G.; Capaldi, C.A. Social Isolation, Loneliness and Positive Mental Health Among Older Adults in Canada During the COVID-19 Pandemic. *Health Promot. Chronic Dis. Prev. Can.* **2023**, *43*, 171–181. [CrossRef]
144. Nalbandian, A.; Sehgal, K.; Gupta, A.; Madhavan, M.V.; McGroder, C.; Stevens, J.S.; Cook, J.R.; Nordvig, A.S.; Shalev, D.; Sehrawat, T.S.; et al. Post-acute COVID-19 syndrome. *Nat. Med.* **2021**, *27*, 601–615. [CrossRef]
145. Thakur, V.; Ratho, R.K.; Kumar, P.; Bhatia, S.K.; Bora, I.; Mohi, G.K.; Saxena, S.K.; Devi, M.; Yadav, D.; Mehariya, S. Multi-Organ Involvement in COVID-19: Beyond Pulmonary Manifestations. *J. Clin. Med.* **2021**, *10*, 446. [CrossRef] [PubMed]
146. Afshar, Z.M.; Pirzaman, A.T.; Karim, B.; Anaraki, S.R.; Hosseinzadeh, R.; Pireivatlou, E.S.; Babazadeh, A.; Hosseinzadeh, D.; Miri, S.R.; Sio, T.T.; et al. SARS-CoV-2 Omicron (B.1.1.529) Variant: A Challenge with COVID-19. *Diagnostics* **2023**, *13*, 559. [CrossRef]

147. Menni, C.; Valdes, A.M.; Polidori, L.; Antonelli, M.; Penamakuri, S.; Nogal, A.; Louca, P.; May, A.; Figueiredo, J.C.; Hu, C.; et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: A prospective observational study from the ZOE COVID Study. *Lancet* **2022**, *399*, 1618–1624. [CrossRef] [PubMed]
148. Relan, P.; Motaze, N.V.; Kothari, K.; Askie, L.; Waroux, O.L.P.d.; Van Kerkhove, M.D.; Diaz, J.; Vijayaraghavan, B.K.T. Severity and outcomes of Omicron variant of SARS-CoV-2 compared to Delta variant and severity of Omicron sublineages: A systematic review and metanalysis. *BMJ Glob. Health* **2023**, *8*, e012328. [CrossRef]
149. Hu, F.-H.; Jia, Y.-J.; Zhao, D.-Y.; Fu, X.-L.; Zhang, W.-Q.; Tang, W.; Hu, S.-Q.; Wu, H.; Ge, M.-W.; Du, W.; et al. Clinical outcomes of the severe acute respiratory syndrome coronavirus 2 Omicron and Delta variant: Systematic review and meta-analysis of 33 studies covering 6 037 144 coronavirus disease 2019–positive patients. *Clin. Microbiol. Infect.* **2023**, *29*, 835–844. [CrossRef]
150. Nyberg, T.; Ferguson, N.M.; Nash, S.G.; Webster, H.H.; Flaxman, S.; Andrews, N.; Hinsley, W.; Bernal, J.L.; Kall, M.; Bhatt, S.; et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: A cohort study. *Lancet* **2022**, *399*, 1303–1312. [CrossRef]
151. Tian, D.; Pan, Y.; Ge, Z.; Kong, X.; Zhang, Y.; Zhang, Q.; Wang, A.; Yang, P.; Chen, Z. Difference of Clinical Characteristics in Patients with Omicron and Delta Variants of SARS-CoV-2 in Beijing, China. *Infect. Dis. Immun.* **2023**, *3*, 75–82. [CrossRef]
152. Lauring, A.S.; Tenforde, M.W.; Chappell, J.D.; Gaglani, M.; A Ginde, A.; McNeal, T.; Ghamande, S.; Douin, D.J.; Talbot, H.K.; Casey, J.D.; et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: Prospective observational study. *BMJ* **2022**, *376*, e069761. [CrossRef] [PubMed]
153. Sahin, A.; Karadag-Oncel, E.; Buyuksen, O.; Ekemen-Keles, Y.; Ustundag, G.; Elvan-Tuz, A.; Tasar, S.; Didinmez-Taskirdi, E.; Baykan, M.; Kara-Aksay, A.; et al. The diversity in the clinical features of children hospitalized with COVID-19 during the nonvariant, Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (B.1.1.529) variant periods of SARS CoV-2: Caution for neurological symptoms in Omicron variant. *J. Med. Virol.* **2023**, *95*, e28628. [CrossRef]
154. Ellul, M.A.; Benjamin, L.; Singh, B.; Lant, S.; Michael, B.D.; Easton, A.; Kneen, R.; Defres, S.; Sejvar, J.; Solomon, T. Neurological associations of COVID-19. *Lancet Neurol.* **2020**, *19*, 767–783. [CrossRef]
155. Fernández-De-Las-Peñas, C.; Notarte, K.I.; Peligro, P.J.; Velasco, J.V.; Ocampo, M.J.; Henry, B.M.; Arendt-Nielsen, L.; Torres-Macho, J.; Plaza-Manzano, G. Long-COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic Review of the Literature. *Viruses* **2022**, *14*, 2629. [CrossRef]
156. Hernández-Aceituno, A.; García-Hernández, A.; Larumbe-Zabala, E. COVID-19 long-term sequelae: Omicron versus Alpha and Delta variants. *Infect. Dis. Now* **2023**, *53*, 104688. [CrossRef]
157. Tziolos, N.-R.; Ioannou, P.; Baliou, S.; Kofteridis, D.P. Long COVID-19 Pathophysiology: What Do We Know So Far? *Microorganisms* **2023**, *11*, 2458. [CrossRef]
158. Mistrulli, R.; Ferrera, A.; Muthukkattil, M.L.; Volpe, M.; Barbato, E.; Battistoni, A. SARS-CoV-2 Related Myocarditis: What We Know So Far. *J. Clin. Med.* **2023**, *12*, 4700. [CrossRef] [PubMed]
159. Ursescu, C.; Teodoru, G.; Bucurica, S.; Nica, R.I.; Lazăr, Ș.D.; Popescu, M.N.; Ciobanu, I.; Berteanu, M. Using the ClinFIT COVID-19 Instrument to Assess the Functional Impairments Specific to Post-COVID-19 Patients in Romania. *Diagnostics* **2024**, *14*, 1540. [CrossRef] [PubMed]
160. Ahuja, S.; Zaheer, S. From COVID-19 to Long COVID: The Forms of the Neurological Manifestations. *J. Mind Med. Sci.* **2023**, *10*, 209–216. [CrossRef]
161. Vasichkina, E.; Alekseeva, D.; Kudryavtsev, I.; Glushkova, A.; Starshinova, A.Y.; Malkova, A.; Kudlay, D.; Starshinova, A. COVID-19 Heart Lesions in Children: Clinical, Diagnostic and Immunological Changes. *Int. J. Mol. Sci.* **2023**, *24*, 1147. [CrossRef] [PubMed]