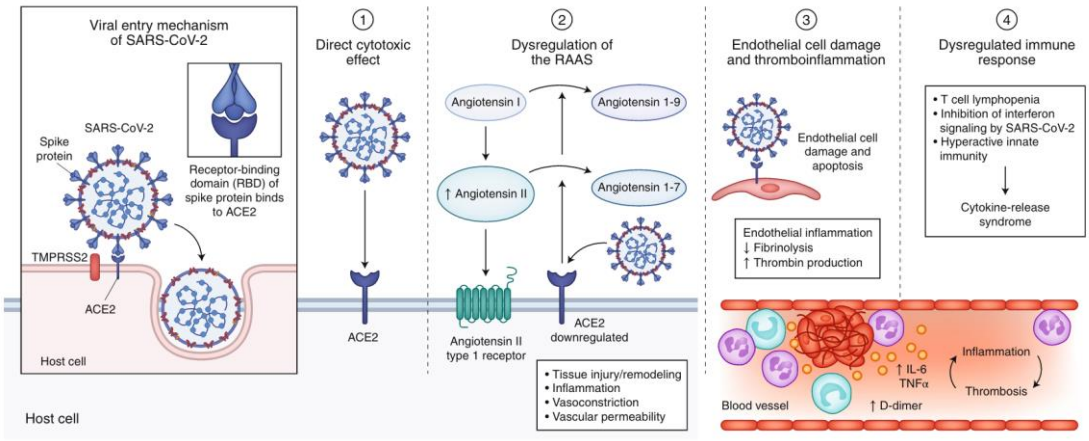
Extrapulmonary manifestations of COVID-19



Fisiopatología de COVID-19. El SARS-CoV-2 ingresa a las células huésped a través de la interacción de su proteína espiga con el receptor de entrada ACE2 en presencia de TMPRSS2 (extremo izquierdo). Los mecanismos propuestos para COVID-19 causados por infección con SARS-CoV-2 incluyen (1) daño celular directo mediado por virus; (2) desregulación del RAAS como consecuencia de la regulación negativa de ACE2 relacionada con la entrada viral, lo que conduce a una disminución de la escisión de angiotensina I y angiotensina II; (3) daño de las células endoteliales y tromboinflamación; y (4) desregulación de la respuesta inmune e hiperinflamación causada por la inhibición de la señalización de interferón por el virus, la linfodepleción de células T y la producción de citocinas proinflamatorias, particularmente IL-6 y TNFα.

Manifestaciones extrapulmonares de COVID-19

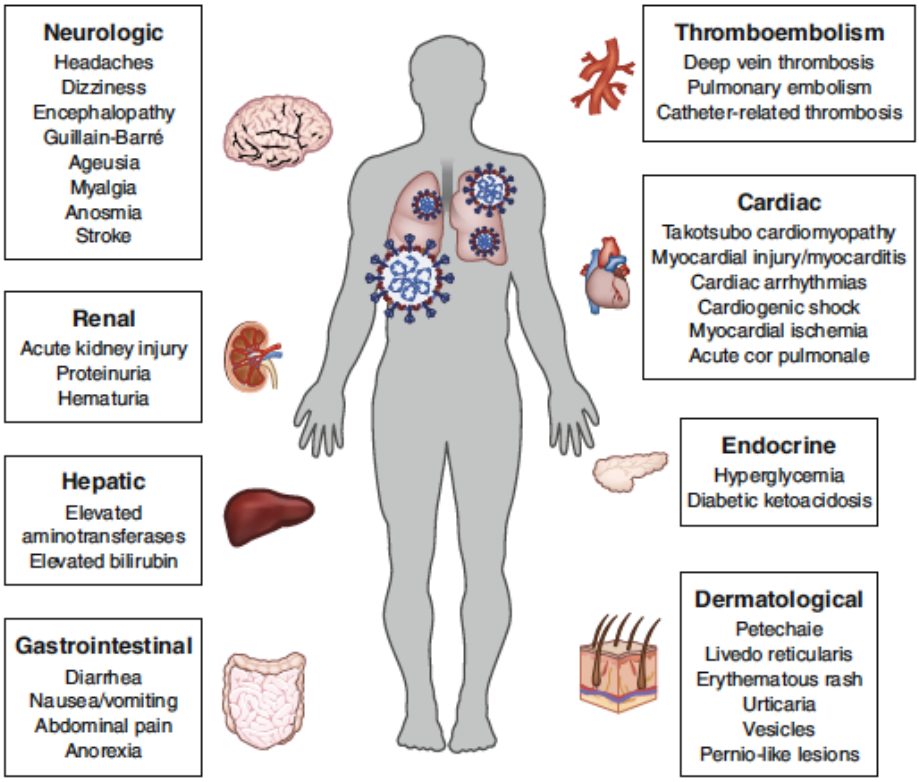
Gupta, A., Madhavan, M.V., Sehgal, K. *et al.* Extrapulmonary manifestations of COVID-19. *Nat Med* **26,** 1017–1032 (2020). https://doi.org/10.1038/s41591-020-0968-3

Disponible en: https://www.nature.com/articles/s41591-020-0968-3.pdf

Antecedente: Es bien conocido que el SARS-CoV-2 cursa como una enfermedad de manifestaciones clínicas sustanciales a nivel pulmonar incluida la neumonía y el síndrome de dificultad respiratoria aguda (SDRA), Durante este periodo se han observado muchas otras manifestaciones extrapulmonares de COVID-19.La literatura emergente sugieren que los sistemas hematológicos, cardiovasculares, renales, gastrointestinales y hepatobiliares, endocrinológicos, neurológicos, oftalmológicos y dermatológicos pueden verse afectados

La COVID-19 puede reflejar la diseminación extrapulmonar y la replicación del SARS-CoV-2, como se ha observado para otros coronavirus zoonóticos, o secuelas inmunopatológicas generalizadas de la enfermedad. Para proporcionar una perspectiva sobre estas manifestaciones extrapulmonares, los autores discuten la fisiopatología y el impacto clínico de COVID-19 en varios sistemas de órganos. La patofisiología SARS-CoV-2 parece emplear mecanismos para el

reconocimiento de receptores similares a los utilizados por coronavirus virulentos anteriores como el SARS-CoV, el patógeno responsable de la epidemia de SARS de 2003 (ref. 8-11). La proteína de pico de coronavirus facilita la entrada del virus en las células objetivo. La subunidad espiga del SARS-CoV y la del SARS CoV-2 comprometen a la ACE2 (enzima convertidora de angiotensina 2) como receptor de entrada (Fig. 1). Además, la entrada celular requiere el cebado de la proteína espiga por la serina proteasa celular TMPRSS2 u otras proteasas12. Se requiere la coexpresión en la superficie celular de ACE2 y TMPRSS2 para completar este proceso de entrada. Además, la eficiencia con la que el virus se une a ACE2 es un determinante clave de la transmisibilidad.



Box 1 | Hematologic and immune system–related manifestations of COVID-19

Clinical presentations

- Laboratory markers:

Cell counts: lymphopenia, leukocytosis, neutrophilia, thrombocytopenia
Inflammatory markers: elevations in erythrocyte sedimentation rate, C-reactive protein, ferritin, IL-6, lactate dehydrogenase
Coagulation indices: elevated D-dimer and fibrinogen; prolonged prothrombin time and partial thromboplastin time

- Arterial thrombotic complications: MI, ischemic stroke, acute limb, and mesenteric ischemia
- Venous thrombotic complications: deep vein thrombosis and pulmonary embolism
- Catheter-related thrombosis: thrombosis in arterial and venous catheters and extracorporeal circuits
- Cytokine-release syndrome: high-grade fevers, hypotension, multi-organ dysfunction

COVID-19-specific considerations

- Perform longitudinal evaluation of cell counts, inflammatory markers, and coagulation indices in hospitalized patients[101]
- Recommend enrollment in clinical trials evaluating the benefit and safety of higher-than-usual prophylactic dose or therapeutic dose in the absence of documented thromboembolism[36]
- If there is evidence of hyperinflammation, consider enrollment in clinical trials investigating the efficacy of targeted inhibitors of inflammatory cytokines of the innate immune system (e.g., IL-6 and IL-1) or their signaling pathways[55]
- Global immunosuppression with corticosteroids may have a role in the setting of critical illness associated with cytokine storm[55]

General considerations

- Perform routine risk assessment for venous thromboembolism for all hospitalized patients
- Strongly consider pharmacological prophylaxis for venous thromboembolism in the absence of absolute contraindications (active bleeding or severe thrombocytopenia)
- Prefer low-molecular-weight heparins or unfractionated heparin over oral anticoagulants in most patients in the inpatient setting
- Consider hepatic and renal function when determining appropriate dose and type of antithrombotic drugs
- Consider post-hospitalization extended thromboprophylaxis on an individual patient basis, particularly for those with a history of critical illness

Box 2 | Cardiovascular manifestations of COVID-19

Clinical presentations

- Myocardial ischemia and MI (type 1 and 2)
- Myocarditis
- Arrhythmia: new-onset atrial fibrillation and flutter, sinus tachycardia, sinus bradycardia, QTc prolongation (often drug induced), torsades de pointes, sudden cardiac death, pulseless electrical activity
- Cardiomyopathy: biventricular, isolated right or left ventricular dysfunction
- Cardiogenic shock

COVID-19-specific considerations

- Do not routinely discontinue ACE inhibitors or ARBs in patients already on them at home; assess on a case-by-case basis[132,133]
- Perform an electrocardiogram or telemetry monitoring for patients at medium to high risk for torsades de pointes who are being treated with QTc-prolonging drugs[138]
- Carefully consider the utility of diagnostic modalities, including cardiac imaging, invasive hemodynamic assessments, and endomyocardial biopsies, to minimize the risk of viral transmission[139,140]
- Primary percutaneous coronary intervention remains preferred approach for most patients with STEMI; consider fibrinolytic therapy in select patients, especially if personal protective equipment is not available[134–136]

General considerations

- Utilize non-invasive hemodynamic assessments, and measurement of lactate, troponin, and beta-natriuretic peptide concentrations, with sparing use of routine echocardiography for guidance about fluid resuscitation, vasoactive agents, and mechanical circulatory support
- Minimize invasive hemodynamic monitoring, but can consider in select patients with mixed vasodilatory and cardiogenic shock
- Consider point-of-care ultrasound to assess regional wall-motion abnormalities to help distinguish type 1 MI from myocarditis
- Early catheterization and revascularization is recommended for high-risk patients with NSTEACS (e.g., GRACE score >140)
- Consider medical therapy for low-risk patients with NSTEACS, particularly if the suspicion for type 1 MI is low
- Monitor and correct electrolyte abnormalities to mitigate arrhythmia risk

Abbreviations: NSTEACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment-elevation MI; GRACE, Global Registry of Acute Coronary Events.

Box 3 | Renal manifestations of COVID-19

Clinical presentations
- AKI
- Electrolyte abnormalities (hyperkalemia, hyponatremia, and hypernatremia, among others)
- Proteinuria
- Hematuria
- Metabolic acidosis
- Clotting of extracorporeal circuits used for RRT

COVID-19-specific considerations
- Evaluate urine analysis and protein-to-creatinine ratio at admission, given the association of proteinuria and hematuria with outcomes[142,154]
- Consider empiric low-dose systemic anticoagulation during the initiation and day-to-day management of extracorporeal circuits for RRT[157]
- Consider co-localization of patients who require RRT and use shared RRT protocols[156]
- Consider acute peritoneal dialysis in select patients to minimize personnel requirements[156]

General considerations
- Individualize fluid-balance strategies guided by markers of volume status (serum lactate, urinary electrolytes, and hemodynamic measures), and of pulmonary, myocardial, and renal function
- Consider continuous RRT in critically ill patients with severe AKI and/or serious or life-threatening metabolic complications that do not respond to medical therapy

Box 4 | Gastrointestinal and hepatobiliary manifestations of COVID-19

Clinical presentations
- Nausea and/or vomiting, diarrhea, abdominal pain, anorexia
- Rare cases of mesenteric ischemia and gastrointestinal bleeding
- Laboratory markers: elevated hepatic transaminases, elevated bilirubin, low serum albumin

COVID-19-specific considerations
- Consider COVID-19 as a differential diagnosis in patients who present with isolated gastrointestinal symptoms in the absence of respiratory symptoms[160]
- If testing resources are scarce, prioritize testing for SARS-CoV-2 among patients who present with both respiratory symptoms and gastrointestinal symptoms[162]
- Use diagnostic endoscopy only for urgent therapeutic reasons (large-volume gastrointestinal bleeding or biliary obstruction)[166,167]
- Monitor hepatic transaminases longitudinally, particularly in patients who are receiving investigational treatments; low-level elevations should not necessarily be considered a contraindication to treatment with these agents[174]

General considerations
- Avoid additional diagnostic tests for aminotransferase elevations less than five times the upper limit of normal unless additional features raise the pre-test probability of actionable findings (hyperbilirubinemia, right upper quadrant pain, hepatomegaly)
- Evaluate other etiologies of abnormal liver biochemistries, including infection with other viruses (such as hepatitis A, B, or C viruses), myositis, cardiac injury and ischemia

Box 5 | Endocrine manifestations of COVID-19

Clinical presentations
- Hyperglycemia
- Ketoacidosis, including that in patients with pre
  agnosed diabetes or no diabetes
- Euglycemic ketosis
- Severe illness in patients with pre-existing dia
  obesity

COVID-19-specific considerations
- Consider checking serum ketones in patients
  glycemia who are on sodium–glucose trans
  inhibitors[177]
- Measure hemoglobin A1C in patients without k
  of diabetes mellitus who present with hyperglyc
  ketoacidosis
- Consider alternative protocols for subcutaneo
  selected patients with mild to moderate diabetic
  on an individual-patient-level basis[192].

General considerations
- Identify and initiate prompt treatment of diabet
  sis with standard protocols in the setting of hyp
- Consider continuous glucose monitors for p
  require an insulin drip (to avoid hourly glucose
- Consider increased insulin dosing in patients b
  with steroids
- Avoid oral hypoglycemic agents due to potent
  for concurrent renal damage (metformin, th
  ones), euglycemic diabetic ketoacidosis (sod
  transport protein inhibitors), cardiac and h
  complications (sulfonylureas), reduced gastric e
  reduced gastrointestinal motility that may cause
  patients require intubation (glucagon-like peptic
  agonists)

Box 6 | Neurologic and ophthalmologic manifestations of COVID-19

Clinical presentations
- Headache, dizziness
- Anosmia, ageusia, anorexia, myalgias, fatigue
- Stroke
- Encephalopathy, encephalitis, Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalopathy
- Conjunctivitis

COVID-19-specific considerations
- Continue adherence to established guidelines for acute ischemic stroke, including thrombolysis and thrombectomy[209]
- Adapt post-acute-care monitoring guidelines for pandemic constraints (most stable patients do not need to be monitored in an ICU for 24 hours)[210]
- Use remote video evaluation, whenever possible, for hospitalized patients with COVID-19 who have symptoms that are of concern for a stroke
- Consider extended-interval or delayed dosing of chronic immunomodulatory therapies in conditions such as multiple sclerosis during COVID-19[211]

General considerations
- Monitor closely for changes in baseline symptoms for vulnerable populations such as elderly patients with Parkinson's disease
- Promptly evaluate any changes in the neurological exam of a hospitalized patient
- Evaluate the risk/benefit balance of off-label uses of tissue plasminogen activator and the empiric use of anticoagulation in critically ill patients (risk of intracranial bleeding and hemorrhagic conversion of stroke)

A destacar:

1. Se realiza una exhaustiva puesta al día de las diferentes manifestaciones clínicas provovadaas por SARV-COV -2
2. A parte de las manifestaciones pulmonares potencialmente mortales de SARS-COV-2, cada vez son mas frecuentes manifestaciones especificas en otros órganos.
3. Hay una necesidad creciente para obtener una compresión integral de la fisiopatologías en órganos específico asi como aquelals manifestaciones multisistemicas
4. Es necesario determinar claramente el mecanismo de diseminación del SARS-COV-2 fuera del tejido pulmonar , así como la contribución de la inmunopatología y el papel que juegan los Anticuerpos en dicho proceso
5. Se necesita conocer los mecanismos identificación de factores que explican la variabilidad en la presentación y la gravedad de la enfermedad.
6. Se necesitan definiciones comunes y la estandarización de los datos en las investigaciones relacionada con COVID-19, transparentes, de calidad y basadas en la evidencias.
7. Este estudio plantea en una tabla de preguntas a nivel fisiopatológico y clínico, para los diferentes órganos y tejidos que se han visto afectados en los pacientes con COVID-19