



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Hyper/neuroinflammation in COVID-19 and suicide etiopathogenesis: Hypothesis for a nefarious collision?

A. Costanza^{a,b,*}, A. Amerio^{c,d}, A. Aguglia^{c,d}, G. Serafini^{c,d}, M. Amore^{c,d}, R. Hasler^{a,e}, J. Ambrosetti^f, G. Bondolfi^{a,b,g}, G. Sampogna^h, I. Berardelliⁱ, A. Fiorillo^h, M. Pompiliⁱ, K. D. Nguyen^{j,k}

^a Department of Psychiatry, Faculty of Medicine, University of Geneva (UNIGE), Geneva, Switzerland

^b Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

^c Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), Section of Psychiatry, University of Genoa, Genoa, Italy

^d IRCCS Ospedale Policlinico San Martino, Genoa, Italy

^e Department of Psychiatry, Service of Psychiatric Specialties, University Hospitals of Geneva (HUG), Geneva, Switzerland

^f Department of Psychiatry and Department of Emergency, Emergency Psychiatric Unit (UAUP), Geneva University Hospitals (HUG), Geneva, Switzerland

^g Department of Psychiatry, Service of Liaison Psychiatry and Crisis Intervention (SPLIC), University Hospitals (HUG), Geneva, Switzerland

^h Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy

ⁱ Sant'Andrea Hospital, "Sapienza" University of Rome, Rome, Italy

^j Tranquis Therapeutics, Palo Alto, CA, USA

^k Department of Microbiology and Immunology, Stanford University, Palo Alto, CA, USA

ARTICLE INFO

Keywords:

COVID-19
 COVID-19 survivors
 Long COVID-19 syndrome
 Suicide
 Suicidal behavior
 Suicidal ideation
 Systemic inflammation
 Hyperinflammation, neuroinflammation
 Cytokines
 Inflammatory peripheral cells, neural cells

ABSTRACT

Accumulating scientific and clinical evidence highlighted pathological hyperinflammation as a cardinal feature of SARS-CoV-2 infection and acute COVID-19 disease. With the emergence of long COVID-19 syndrome, several chronic health consequences, including neuropsychiatric sequelae, have gained attention from the public and medical communities. Since inflammatory mediators have also been accredited as putative biomarkers of suicidal ideations and behaviors, hyper- and neuroinflammation might share some colliding points, overlapping and being interconnected in the context of COVID-19. This review aims to provide a summary of current knowledge on the molecular and cellular mechanisms of COVID-19-associated hyper/neuroinflammation with focus on their relevance to the inflammatory hypothesis of suicide development. Subsequently, strategies to alleviate COVID-19 hyper/neuroinflammation by immunomodulatory agents (many of which at experimental stages) as well as psychopharmacologic/psychotherapeutic approaches are also mentioned. While suicide risk in COVID-19 survivors - until now little known - needs further analysis through longitudinal studies, current observations and mechanistic postulates warrant additional attention to this possibly emerging mental health concern.

1. Introduction

From an outbreak of pneumonia-like respiratory illnesses in Wuhan, China at the end of 2019, the SARS-CoV-2 (COVID-19) has rapidly become a pandemic of immense public health concern. By early September 2021, more than 220 million people had been diagnosed with SARS-CoV-2 infection and more than 4.5 million people have succumbed to this infection (World Health Organization, 2021). Due to the rapidly mutating and highly infectious nature of COVID-19, most global public health initiatives focused their efforts on an accelerated

development of preventative measures, diagnostic methods, and novel treatments. In this regard, several strategies, including vaccination, have been researched and refined for the prevention, detection, and control of COVID-19 (Majumder and Minko, 2021).

Besides these remarkable medical breakthroughs, a growing body of scientific literature has detailed several emerging COVID-19-related psychiatric complications, including increased suicide risk (Fiorillo and Gorwood, 2020; Vindegaard and Benros, 2020). In this context, a possible increase in suicide risk during the early stages of the pandemic had been predicted by the scientific community, due to the contribution

* Correspondence to: Department of Psychiatry, Faculty of Medicine, University of Geneva (UNIGE), Rue Michel-Servet 1, 1211 Geneva, CH.

E-mail address: alessandra.costanza@unige.ch (A. Costanza).

¹ ORCID: <https://orcid.org/0000-0001-6387-6462>.

of various interacting psychosocial factors (e.g., isolation, entrapment, substance abuse, financial stressors) and pre-existing psychiatric illnesses such as depression and history of suicidal crisis (Gunnell et al., 2020; Niederkrotenthaler et al., 2020; Reger et al., 2020; Sher, 2020a; Amerio et al., 2020; Costanza et al., 2020a). During the first wave of COVID-19, worldwide case reports and observational studies from psychiatric emergency departments documented an increase in suicidal ideation (SI) and behavior (SB) (Aly et al., 2020; Berardelli et al., 2020; Goyal et al., 2020; Liu et al., 2020; Mamun and Griffiths, 2020; Pirnia et al., 2020; Thakur and Jain, 2020; Ambrosetti et al., 2021a; Boldrini et al., 2021; Montalbani et al., 2021). However, these early findings could not be substantiated in more recent systematic reviews, meta-analyses, and time-series analyses (John et al., 2020; Kahil et al., 2021; Leske et al., 2021; Phiri et al., 2021; Pirkis et al., 2021). Compared to the pre-pandemic situation, only one meta-analysis reported increased SI and SB during the first pandemic's wave (Dube et al., 2021). On the contrary, the general population was more vulnerable to SI and SB development during later stages of the pandemic (Balestrieri et al., 2021; McIntyre et al., 2021). A possible explanation for this phenomenon may be the persistent and long-lasting impact of various psychosocial factors (Zortea et al., 2020), including the evolution of the global economic crisis (Sher, 2020b; Ambrosetti et al., 2021b; Costanza et al., 2021a; Pompili, 2021). Besides, the increase in suicide risk during the later stages of the pandemic might result from direct chronic biological consequences of the infection, including its hallmark pathology of hyperinflammation (Sher, 2021), defined as the rapid proliferation of effector immune cell subsets and the excessive production of a multitude of pro-inflammatory cytokines by both immune and parenchymal cells.

Given the emerging implications of systemic and neuro-inflammatory processes in the development of SI and SB (Sher, 2021) and recent evidence of mental health deterioration in subjects with long COVID-19 syndrome (Brundin et al., 2017), it is possible that an elevated suicide risk might exist in COVID-19 survivors (Sher, 2020b, 2021). In light of this perspective, this review aims to highlight the current knowledge on COVID-19 associated-hyperinflammation and its possible involvement in SI/SB development.

2. Cellular mediators of COVID-19 associated hyperinflammation

A cardinal feature of SARS-CoV2 infection is the presence of a systemic inflammatory milieu called cytokine storm, including IL1, IL6, IL12, IL18, CCL2, CCL5, GM-CSF, TNF α , and IFN γ , storm (Arunachalam et al., 2020; Garcia-Beltran et al., 2021; Hadjadj et al., 2020; Lucas et al., 2020). Since ACE2, the cellular entry receptor of SARS-CoV2, is widely expressed in various tissues, including the brain, direct infection of vulnerable parenchymal cell subsets by SARS-CoV2 could result in dysregulated peripheral tissue inflammation as well as neurological complications in COVID-19 patients (Bridges et al., 2021; Chen, Wu et al., 2020; Hensley et al., 2021; Ngo et al., 2021; Ziegler et al., 2020). While the hyperinflammatory syndrome in SARS-CoV2 infection is contributed by various effector cell types, emerging evidence has pointed to a critical participation of major innate immune cell subsets of both peripheral and CNS origins in this pathology.

2.1. Monophagocytes

The monophagocyte system consists of several subsets of circulating monocytes and tissue macrophages (Hussell and Bell, 2014; Kapellos et al., 2019; Ziegler-Heitbrock et al., 2010). In the context of SARS-CoV2 infection, the presence of ACE2 on monocytes and macrophages render them susceptible to this respiratory pathogen in both animal models and clinical specimens (Abassi et al., 2020; Bao et al., 2020; Zhao et al., 2020). The contribution of these cells to pathological inflammation observed in COVID-19 patients have been suggested by several important clinical observations that emerged during the early phase of the

pandemic. First, patients with severe COVID-19 disease are characterized by elevation of circulating inflammatory markers such as IL1, IL6, IL8, TNF α , all of which are chiefly derived from monocytes and macrophages (Huang et al., 2020). Second, the increased susceptibility of males to severe COVID-19 development is correlated high levels of innate immune cytokines such as IL8 and IL18 (Takahashi et al., 2020). Third, a multisystem inflammatory syndrome has been documented in pediatric COVID-19 patients, which shares striking clinical presentation with Kawasaki disease and macrophage activation syndrome (Dufort et al., 2020; Feldstein et al., 2020). Lastly, post-mortem histopathological analysis of COVID-19 patients revealed the presence of monophagocyte infiltrate and inflammatory activation in a multisystem manner (Bryce et al., 2021; Carsana et al., 2020; Fox et al., 2020; Gustine and Jones, 2021). Altogether, these findings suggest a pivotal involvement of aberrant activation of the monophagocyte system in COVID-19 hyperinflammatory syndrome.

Following these findings, mechanistic studies have attempted to delineate the relative contribution of circulating monocytes and tissue macrophages to the hyperinflammatory state in COVID-19 (Giamarellos-Bourboulis et al., 2020; Grant et al., 2021; Schulte-Schrepping et al., 2020; Szabo et al., 2021; Zhou et al., 2020). High resolution single cell analysis of the bronchial alveolar lavage fluid from COVID-19 patients demonstrated that lung macrophages resemble a subset of monocytes in the blood, prompting the possibility of sequential recruitment and in situ differentiation of these circulating precursor cells (Liao et al., 2020; Sánchez-Cerrillo et al., 2020). Furthermore, the bronchial alveolar lavage fluid samples from severe COVID-19 patients are also enriched for the monocyte chemoattractants, CCL2 and CCL7 (Zhou, Ren et al., 2020), suggesting that these might play an instrumental role in the recruitment of circulating inflammatory monocytes to the lung of patients with severe illness (Fig. 1A).

2.2. Mast cells

Mast cells are long-lived innate immune cells that not only provide the first line of host defense against viral and bacterial infections but also participate in the pathogenesis of allergic inflammation and neurological disorders (Georgin-Lavialle, Moura et al., 2016; Hendrikus et al., 2017). Emerging evidence has pointed to an involvement of mast cells in inflammatory syndrome associated with COVID-19 (Tan et al., 2021; Conti et al., 2020). Mast-cell-enriched mediators, such as carboxypeptidase A3, chymase, tryptase, and serotonin, were elevated in sera of SARS-CoV2 infected patients and positively correlated with hyperinflammatory markers (Soria-Castro et al., 2021; Gebremeskel et al., 2021). In lung tissues of COVID-19 patients, post-mortem analysis revealed extensive presence of CD117 + mast cells that colocalized with IL1 and TNF α (Ribeiro Dos Santos Miggiolaro et al., 2020). Interestingly, this mast cell activation signature was absent in tissue samples from patients with H1N1 infection as well as health control subjects, highlighting the potential unique involvement of mast cells in COVID-19 (Motta Junior et al., 2020). Several mechanisms by which these cells become activated have been proposed (Gebremeskel et al., 2021; Motta Junior et al., 2020). Notably, a major mast cell-derived mediator, histamine, might play a pivotal role in the initiation of cytokine storm syndrome in COVID-19 patients due to its ability to trigger production of IL1, IL6, IL8, and several other inflammatory chemokines/cytokines (Motta Junior et al., 2020) (Fig. 1B). Last but not least, mast cell activation syndrome (MCAS) has been considered as a potential risk factor for the development of severe SARS-CoV2 infection as its prevalence closely corresponds to the estimated frequency of severe COVID-19 (Frieri, 2015; Molderings et al., 2010; Afrin et al., 2020). This multisystem syndrome is known to escalate shortly after exposure to an immunological stressor, such as infection or allergen, and therefore might represent an important driver of hyperinflammation in COVID-19 patients (Kempuraj et al., 2020a, 2020b; Romero-Sánchez et al., 2020).

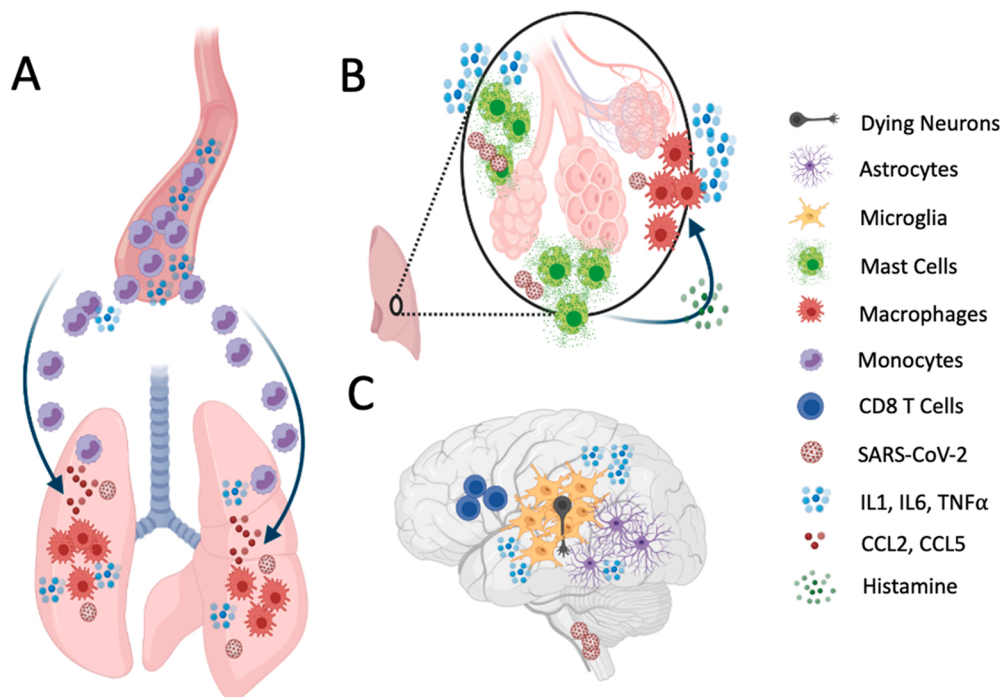


Fig. 1. Cellular mechanisms of COVID-19 hyperinflammation. **A.** SARS-CoV2-activated alveolar macrophages produce both inflammatory mediators, such as IL1, IL6, and TNF α , and chemotactic molecules, such as CCL2/CCL5 to recruit circulating blood monocytes to the airways, amplifying respiratory hyperinflammation. **B.** SARS-CoV2-activated mast cells orchestrate airway hyperinflammation by secreting inflammatory cytokines and activating of alveolar macrophages via their production of histamines. **C.** Upon neuroinvasion of SARS-CoV2, dying neurons are surrounded by activated microglia, which serve as the communicating hub to sustain neuroinflammation by their production of inflammatory mediators and subsequent activation of astrocytes and CD8 + T cells.

2.3. Glial cells

Microglia have been considered a central regulator of neuroinflammation via their production of various neurotoxic and inflammatory mediators such as IL1, IL6, and TNF α (Ajami et al., 2007; Ginhoux et al., 2010). Besides microglia, astrocytes are another major cell type that contribute to inflammatory reactions in the CNS (Linnerbauer et al., 2020). The earliest studies of neurotropic impact of SARS-CoV2 infection have documented meningoencephalitis and brainstem/olfactory bulb dysfunctions in COVID-19 patients, suggesting the presence of neuroinflammatory processes (Manganelli et al., 2020; Whitcroft and Hummel, 2020; Mondal et al., 2021; Yang et al., 2021). Transcriptomic analysis of cellular repertoire in the choroid plexus and cortices of COVID-19 patients also revealed marked perturbations in pathways associated with inflammation and viral entry at this CNS barrier (Pellegrini et al., 2020). In the brain parenchyma, several post-mortem histological studies revealed intense microgliosis nodules in various brain regions and perivascular spaces in majority of COVID-19 patients (Matschke et al., 2020; Schurink et al., 2020; Lee et al., 2021; Schwabenland et al., 2021). Notably, microgliosis was accompanied by their expression of various markers of inflammation (IL-1, IL-6, HLA-DR), suggesting an activated phenotype of these resident CNS immune cells (Matschke et al., 2020; Boroujeni et al., 2021; Lee et al., 2021; Poloni et al., 2021). These activated microglia were found to be in contact with astrocytes, CD8 + cytotoxic T lymphocytes, or surrounding dying neurons (neuronophagia), suggesting that these CNS innate immune cells are the communicating hub that orchestrates neuroinflammation (Fig. 1C). Astrocyte reactivity was also present in COVID-19 patients as evidenced by both histological and serological findings. In this regard, astrogliosis was detected in the brain samples of COVID-19 patients (Matschke et al., 2020; Lee et al., 2021; Reichard et al., 2020). Similarly, a serum indicator of astrogliosis, S100b, was also elevated in moderate to severe COVID-19 patients and positively correlates with markers of inflammation (Aceti et al., 2020; Kanberg et al., 2021). Altogether, these findings highlight the central roles of these glial cell population in the initiation and propagation of inflammatory processes associated with SARS-CoV2 neuroinvasion.

3. Hyperinflammation as an etiological contributor to increased suicide risk in COVID-19?

Besides the immediate impact on COVID-19 pathology, immune-mediated hyperinflammation might also exert long-term health consequences on COVID-19 survivors. In fact, chronic comorbidities of virally infected survivors have been observed in previous pandemics and are particularly relevant for subjects experiencing long COVID-19 syndrome (Chacko et al., 2020; Rogers et al., 2020; Troyer et al., 2020). Among these complications, conditions of psychiatric nature, such as SI and SB are of immense public health concerns.

3.1. Inflammatory signature in suicide pathophysiology

As one of the most prominent causes of mortality in the world, suicide has a complex etiology that has been postulated to be the result of dynamic interplays between psychological stressors and neurobiological risks. Stressors from the environment (such as negative societal, familial and personal occurrences) and consequent hopelessness might constitute the triggering events for most suicidal acts while underlying neurobiological abnormalities might foster suicide vulnerability (Grunebaum et al., 2006; Aguglia et al., 2019b, Zortea, 2020, Aguglia et al., 2021a). While mood disorders, such as depression, have been frequently associated with increased suicide risk, several post-mortem studies and vivo studies of suicidal subjects have provided important insights on putative neurobiological origins of this psychiatric condition (Hawton and van Heeringen, 2009; Mann and Currier, 2010; Costanza et al., 2015; Turecki and Brent, 2016; Turecki et al., 2019; Costanza et al., 2020b). For instance, numerous biochemical and genetic indicators of suicide risks have been documented, including alterations in serotonergic, BDNF, and kynurenine signaling as well as other neurometabolic pathways (Sublette et al., 2011; Costanza et al., 2013; Aguglia et al., 2019a).

Besides these neurobiological factors, pathological inflammation has recently emerged as a potentially significant risk factor for SI/SB development and is of high relevance in the context of COVID-19 (Serafini et al., 2013; Black and Miller, 2015; Courtet et al., 2015; Miná et al., 2015; Ganança et al., 2016; Serafini et al., 2020; Aguglia et al.,

2021b). To date, most studies implicate inflammation, mediated by both soluble factors (IL1, IL6, and TNF α) and abnormally activated cell populations (monophagocytes and glial cells), in the pathophysiology of suicide (Fig. 2). In this regard, several studies have documented an association of various biomarkers of inflammation with suicide risk. Genetic analyses of suicidal subjects revealed an association between IL6, IL8, and TNF α and increased risk for suicidal attempts (SA) (Kim et al., 2013; Knowles et al., 2019). Additionally, IL6, TNF α , and CRP have been found to be abnormally elevated in sera samples of depressed suicide attempters (Aguglia et al., 2020). Corroborating findings from several meta-analyses also demonstrated that subjects with active SI and past history of SA also exhibited higher circulating levels of IL1 and IL6 (Black and Miller, 2015; Ducasse et al., 2015). In the CNS microenvironment, IL6 was found to be elevated in the cerebrospinal fluid of suicide attempters and correlated with a history of violent suicidal acts and depression scores (Lindqvist et al., 2009). This inflammatory cytokine expression in the CSF also correlated with suicidal risk in patients with depressive symptoms (Bay-Richter et al., 2015). Consistent with these fluid biomarker studies, post-mortem analyses of brain samples from suicidal subjects showed that IL1, IL6, and TNF α were elevated in various regions of the prefrontal cortex, pointing to the possible involvement of neuroinflammation in SI/SB development (Pandey et al., 2018; Wang et al., 2018).

While some contradictory observations for the involvement of selected inflammatory mediators in SI/SB development warrant further confirmatory analyses (Kim et al., 2008; Gabbay et al., 2009; Grassi-Oliveira et al., 2012; Coryell et al., 2018), it's worth noting that these effector molecules are chiefly produced by peripheral innate immune cells and CNS glia, supporting the possible involvement of these cell types in this phenomenon (Baharikhooob and Kolla, 2020). In fact, a proinflammatory phenotype of circulating monocytes has been observed in blood samples of depressed suicidal subjects (Nowak et al., 2019). Elevated frequencies of blood monocytes and granulocytes have also been linked with increased suicide risk (Keaton et al., 2019). Similarly, macrophage infiltration into the brain parenchyma of depressed suicides has been noted by elevated expression of CD45, Iba1 as well as a classical macrophage chemoattractant, CCL2 (Torres-Platas et al., 2014). Astrocytic hypertrophy has also been observed in the anterior cingulate,

thalamus, and caudate regions of depressed suicidal subjects. Furthermore, astrogliosis and microgliosis were observed in selected brain regions of suicide victims, suggesting widespread neuroinflammation might not be necessary to precipitate an increased risk for suicide (Schlicht et al., 2007; Steiner et al., 2008; Torres-Platas et al., 2011; Schnieder et al., 2014; Torres-Platas et al., 2014; Torres-Platas et al., 2015; Cabrera et al., 2019). One prominent hypothesis suggests that inflammatory milieu produced by CNS macrophages and glial cells might cause specific induction of serotonergic and glutamatergic neurotoxicity (Pompili et al., 2017; Suzuki et al., 2019). Alternatively, inflammatory mediators might directly induce neurotoxicity and/or excitotoxicity in vulnerable neuroanatomical circuits that have been implicated in SI/SB development.

3.2. COVID-19 associated inflammation as a suicide risk factor?

While long term analysis of suicide risk in COVID-19 patients is absent, emerging evidence has brought attention to the possible impact of COVID-19 on suicide risks of the infected. In fact, in a 6-month study of 40469 patients who were diagnosed with COVID-19 infection, 22.5% were presented with neuropsychiatric co-morbidities, including SI (Nalleballe et al., 2020). Another study of 16315 young adults diagnosed with COVID-19 in the US revealed a 13.4% rate of SI and 1.3% rate of SA, which are both positively correlated with disease severity (DeVylder et al., 2021). Notably, suicide risk might be elevated in infected subjects with a history of SI. As demonstrated in a study of US veterans, those who were infected with SARS-CoV2 were more likely to exhibit peri-pandemic SI, whose strongest independent predictive factors include the existence of this neuropsychiatric symptom before the pandemic (Na et al., 2021).

Recent studies have delineated the contribution of major innate immune cell subsets relevant to COVID-19 associated hyperinflammatory pathology to specific psychiatric risk factors of suicide (Fig. 2). In this regard, mast cell activation has been shown to be associated with depression (Moura et al., 2011; Moura et al., 2012; Georjin-Lavialle, Gaillard et al., 2016; Georjin-Lavialle, Moura et al., 2016), one of the strongest risk factors for suicide (Coughlin and Sher, 2013, CDC USA.gov 2020). Therefore, dysregulated mast cell activity as

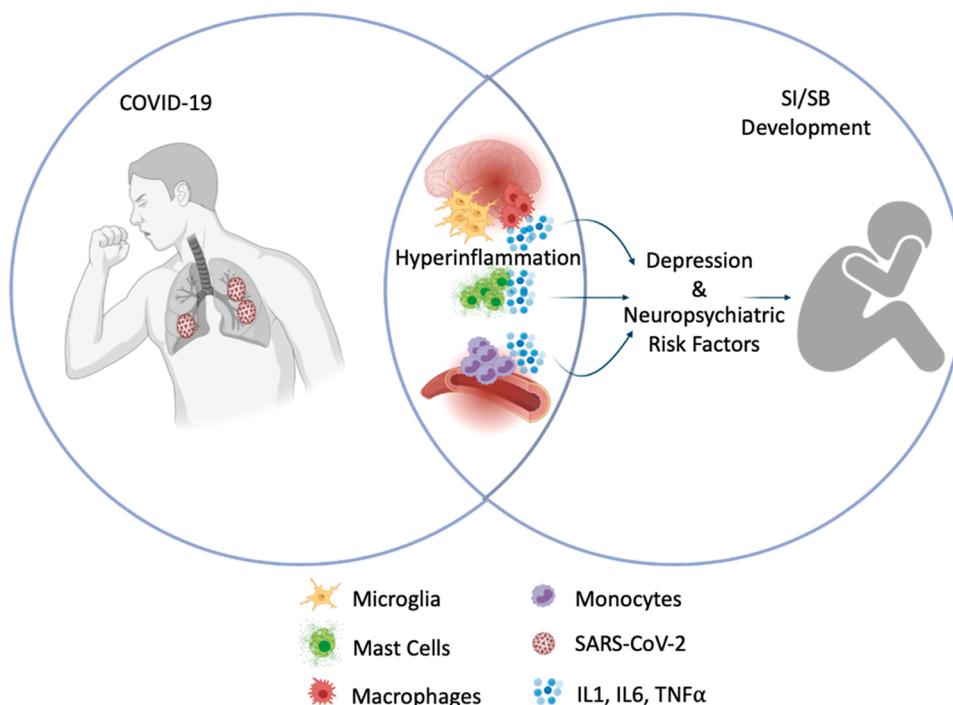


Fig. 2. Hyperinflammation as the possible colliding point between COVID-19 and SI/SB development. *Hyperinflammation in COVID-19 is characterized by activation of several immune cell types in the circulation/peripheral tissues (monocytes and mast cells) as well as in the central nervous system (microglia and macrophages). These inflammatory mediators have been linked to depression and other neuropsychiatric risk factors of SI/SB development, prompting the possible presence of hyperinflammation as the precipitating factor for increased suicide risk in COVID-19 survivors.*

a result of SARS-CoV2 infection might heighten the risk for depression-related SI/SB development. Other studies have also documented the presence of several neuroinflammation-associated comorbidities in COVID-19 patients, including stroke, headache, and depression, all of which are independently associated with increased suicide risk (Coughlin and Sher, 2013; Hudzik and Marek, 2014; Asadi-Pooya and Simani, 2020; Mazza et al., 2020; Steardo et al., 2020). Lastly, the overlapping presentation of psychosis and depression with peripheral monophagocyte activation as well as increased suicide vulnerability also suggests the possible existence of a common inflammatory pathway by which the monophagocyte system contributes to the development of this complex neuropsychiatric phenomenon (Maes et al., 1992; Bergink et al., 2014). Along with previous implications of the role of several soluble mediators (IL1, IL6, and TNF α) in both SI/SB development and COVID-19 hyperinflammation, these collective findings point to the possibility that COVID-19 survivors might be at a higher risk for this neuropsychiatric condition.

4. Inflammation as a therapeutic target in COVID-19 and its relevance to suicide prevention

4.1. Anti-inflammatory therapies for COVID-19

Several treatment modalities for COVID-19 have been developed to address major drivers of pathological inflammation in this disease. IL6 represents one of the most attractive therapeutic targets for COVID-19 as serum levels of this inflammatory cytokine have been shown to be a reliable biomarker for cytokine storm syndrome and disease severity (Chen et al., 2021; Leisman et al., 2021). A series of inhibitors of IL6 signaling, which is present in inflammatory monocytes and macrophages, are in various phases of clinical trials for severe COVID-19 patients (Alattar et al., 2020; Sciascia et al., 2020; Xu et al., 2020; Sieper et al., 2015; Eskandary et al., 2019; Meira et al., 2021). Trials to evaluate blockade of other inflammatory cytokines such as TNF α and IL1 are also in progress (Cavalli et al., 2020; Feldmann et al., 2020; Huet et al., 2020; Robinson et al., 2020). Chemokines which orchestrate the recruitment and accumulation of monophagocytes also represent an alternative class of inflammatory targets for COVID-19 patients (Zhao, 2010; Patterson et al., 2020). Additionally, mast cell stabilizers or modulators of secreted inflammatory products from mast cells are attractive therapeutics for COVID-19 (Kazama, 2020; Hafezi et al., 2021; Wu et al., 2020; Zhou et al., 2015). These modulators of mast cell function have either been proposed for or currently in trials for COVID-19. On the other hand, treatments focusing on resolving neuroinflammation in COVID-19 have not yet been evaluated in the clinics. However, candidate inhibitors of microglial activation have been proposed to mitigate the impact of neuroinflammation-associated pathology in COVID-19 patients (Chaves Filho et al., 2021; Kempuraj et al., 2020a, 2020b).

While inhibitors of specific inflammatory pathways have shown both promising clinical results and/or provided novel mechanistic insights into their relative contribution to COVID-19 associated cytokine storm syndrome, other strategies to broadly suppress hyperinflammation have also been attempted, including JAK1/2 and BTK inhibitors (Cantini et al., 2020; Richardson et al., 2020; Convertino et al., 2020; Kalia-murthi et al., 2021; Stack et al., 2021). Additionally, clinically approved drugs that have been shown to be effective in suppressing systemic or tissue inflammation (particularly the respiratory tract), such as tacrolimus, sirolimus, prednisolone, and dexamethasone, are also under investigation (Moutsopoulos et al., 2018). Lastly, neuropsychiatric medications, including risperidone, paliperidone, olanzapine, aripiprazole, that possess dual anti-inflammatory and anti-psychotic properties, have been trialed in COVID-19 patients with high risk for psychiatric complications (Canal-Rivero et al., 2021; Crespo-Facorro et al., 2021; Tendilla-Beltrán and Flores, 2021).

4.2. Therapeutic considerations for anti-inflammatory treatments in suicide prevention

As discussed above, efforts to address inflammatory pathology in COVID-19 have provided promising results. However, whether or not suppressing inflammation could provide protection against SI/SB development and other psychiatric comorbidities remains to be investigated. Notably, a recent study has demonstrated the potential efficacy of anti-inflammatory medication in reducing risks of SI, providing the first proof of concept for targeting inflammatory pathways in suicide prevention (Lehrer and Rheinstein, 2019). However, some associations between suicide risk and anti-inflammatory therapies have been reported. In this regard, the controversial usage of the anti-malarial drug, hydroxychloroquine, in COVID-19 patients has been linked to significant cardiotoxicity and other neuropsychiatric complications, including suicide (Ahmadizar et al., 2020; Boulware et al., 2020; Cavalcanti et al., 2020; Hamm and Rosenthal, 2020; Ong et al., 2021; Costanza et al., 2021c). In light of this clinical experience, possible risk of suicide must be carefully examined for all anti-inflammatory therapies, in the context of suicide prevention for COVID-19 survivors.

Beside anti-inflammatory therapies, psychiatric assessment, which has been shown to be highly effective in suicide prevention, must also be provided to the survivors of COVID-19. Patient assessment for this suicide risk factor after COVID-19 recovery should be considered (Sher, 2020a). Such evaluation often requires consistent post COVID-19 follow-ups in the presence of an interdisciplinary team of neurologists, psychiatrists, and psychologists (Sher, 2020a). Special attention must be provided to COVID-19 patients with history of SI and SB, depression, psychotic disorders as well as emerging evidence of impulsivity, emotional lability, irritability, anger and apathy (Baertschi et al., 2019; Costantini et al., 2021; Costanza et al., 2021b). Information from these clinical assessments may help identify specific targets for both psychopharmacologic and psychotherapeutic interventions so that a comprehensive care program could be provided to COVID-19 survivors (Costanza et al., 2020a; Postolache et al., 2021). Furthermore, the interactive nature of these psychotherapeutic targets could also address the psychological needs for caregivers and family members of COVID-19 survivors. Lastly, psychotherapy has emerged as a novel modulator of immune-related health (Shields et al., 2020). In this regard, recent studies have demonstrated that cognitive behavioral interventions could suppress the elevated expression of various inflammatory markers in both somatic illnesses and psychiatric conditions (Nemirovsky et al., 2021; Diaz et al., 2021; Sundquist et al., 2021). The direct impact of psychosocial interventions on excessive immune activation provides another line of support for the use of this modality against COVID-19-associated hyperinflammation and its possible sequelae of increased suicide risk.

5. Conclusion

Hyperinflammation, a central orchestrator of SARS-CoV2 pathogenesis, is a possible contributing factor to the development of a wide range of chronic neuropsychiatric complications, including suicide, in COVID-19 survivors. While it remains unknown to which extent anti-inflammatory therapies might be efficacious in preventing the development of these conditions, these observations above suggest that an integrated and multidimensional research efforts should be implemented to address this emerging unmet medical need. In addition, both pharmacological and psychotherapeutic interventions should be promptly designed and evaluated in anticipation of a possible increase in suicide risk in COVID-19 survivors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest

KDN is the scientific founder of Tranquis Therapeutics, a biotechnology company that develops novel treatments for neuroinflammatory and neurodegenerative diseases. KDN also serves a scientific advisor for Tochikunda, biotechnology company that develops SARS-CoV-2 diagnostic devices. All other authors declare no conflict of interest.

Data Availability

Data will be made available on request.

Acknowledgements

This work was developed within the framework of the Department of Excellence of MIUR (Law 232/2016).

References

- Abassi, Z., Knaney, Y., Karram, T., Heyman, S.N., 2020. The lung macrophage in SARS-CoV-2 infection: a friend or a foe? *Front Immunol.* 11 <https://doi.org/10.3389/fimmu.2020.01312>.
- Aceti, A., Margarucci, L.M., Scaramucci, E., Orsini, M., Salerno, G., Di Sante, G., et al., 2020. Serum S100B protein as a marker of severity in Covid-19 patients. *Sci. Rep.* 10 (1) <https://doi.org/10.1038/s41598-020-75618-0>.
- Afrin, L.B., Weinstock, L.B., Molderings, G.J., 2020. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int. J. Infect. Dis.* 100, 327–332. <https://doi.org/10.1016/j.ijid.2020.09.016>.
- Aguglia, A., Solano, P., Giacomini, G., Caprino, M., Conigliaro, C., Romano, M., et al., 2019a. The association between dyslipidemia and lethality of suicide attempts: a case-control study. *Front Psychiatry* 10, 70. <https://doi.org/10.3389/fpsy.2019.00070>.
- Aguglia, A., Serafini, G., Solano, P., Giacomini, G., Conigliaro, C., Salvi, V., et al., 2019b. The role of seasonality and photoperiod on the lethality of suicide attempts: a case-control study. *J. Affect. Disord.* <https://doi.org/10.1016/j.jad.2018.12.094>.
- Aguglia, A., Solano, P., Parisi, V.M., Asaro, P., Caprino, M., Trabucco, A., et al., 2020. Predictors of relapse in high lethality suicide attempters: a six-month prospective study. *J. Affect. Disord.* 271, 328–335. <https://doi.org/10.1016/j.jad.2020.04.006>.
- Aguglia, A., Giacomini, G., Montagna, E., Amerio, A., Escelsior, A., Capello, M., et al., 2021a. Meteorological variables and suicidal behavior: air pollution and apparent temperature are associated with high-lethality suicide attempts and male gender. *Front Psychiatry* 5;12:653390. <https://doi.org/10.3389/fpsy.2021.653390>.
- Aguglia, A., Amerio, A., Asaro, P., Caprino, M., Conigliaro, C., Giacomini, G., et al., 2021b. High-lethality of suicide attempts associated with platelet to lymphocyte ratio and mean platelet volume in psychiatric inpatient setting. *World J. Biol. Psychiatry* 22 (2), 119–127. <https://doi.org/10.1080/15622975.2020.1761033>.
- Ahmadizar, F., Soroush, N., Ikram, M.A., Kors, J.A., Kavousi, M., Stricker, B.H., 2020. QTc-interval prolongation and increased risk of sudden cardiac death associated with hydroxychloroquine. *Eur. J. Prev. Cardiol.*, zwaa118. <https://doi.org/10.1093/eurjpc/zwaa118>.
- Ajami, B., Bennett, J.L., Krieger, C., Tetzlaff, W., Rossi, F.M.V., 2007. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nat. Neurosci.* 10 (12), 1538–1543. <https://doi.org/10.1038/nn2014>.
- Alattar, I., Ibrahim, T.B.H., Shaar, S.H., Abdalla, S., Shukri, K., Daghfal, J.N., et al., 2020. Tocilizumab for the treatment of severe coronavirus disease 2019. *J. Med. Virol.* 92 (10), 2042–2049. <https://doi.org/10.1002/jmv.25964>.
- Aly, L., Sondergeld, R., Holzle, P., Frank, A., Knier, B., Pausch, E., et al., 2020. [The COVID-19 pandemic has not changed the number but the type of psychiatric emergencies: a comparison of care data between 2019 and 2020]. *Nervenarzt* 91 (11), 1047–1049. <https://doi.org/10.1007/s00115-020-00973-2>.
- Ambrosetti, J., Macheret, L., Folliet, A., Wullschlegler, A., Amerio, A., Aguglia, A., et al., 2021a. Impact of the COVID-19 pandemic on psychiatric admissions to a large swiss emergency department: an observational study. *Int. J. Environ. Res. Public Health* 18 (3). <https://doi.org/10.3390/ijerph18031174>.
- Ambrosetti, J., Macheret, L., Folliet, A., Wullschlegler, A., Amerio, A., Aguglia, A., et al., 2021b. Psychiatric emergency admissions during and after COVID-19 lockdown: short-term impact and long-term implications on mental health. *BMC Psychiatry* 21 (1), 465. <https://doi.org/10.1186/s12888-021-03469-8>.
- Amerio, A., Aguglia, A., Odone, A., Gianfredi, V., Serafini, G., Signorelli, C., Amore, M., 2020. Covid-19 pandemic impact on mental health of vulnerable populations. *Acta Biomed.* 95–96. <https://doi.org/10.23750/abm.v91i9-s.10112>.
- Arunachalam, P.S., Wimmers, F., Mok, C.K.P., Perera, R.A.P.M., Scott, M., Hagan, T., et al., 2020. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* 369 (6508), 1210–1220. <https://doi.org/10.1126/science.abc6261>.
- Asadi-Pooya, A.A., Simani, L., 2020. Central nervous system manifestations of COVID-19: a systematic review, 116832-116832 *J. Neurol. Sci.* 413. <https://doi.org/10.1016/j.jns.2020.116832>.
- Baertschi, M., Costanza, A., Canuto, A., Weber, K., 2019. The dimensionality of suicidal ideation and its clinical implications. *Int. J. Methods Psychiatr. Res.* 28 (1), e1755 <https://doi.org/10.1002/mpr.1755>.
- Baharikhooob, P., Kolla, N.J., 2020. Microglial dysregulation and suicidality: a stress-diathesis perspective. *Front Psychiatr.* 11 <https://doi.org/10.3389/fpsy.2020.00781>.
- Balestrieri, M., Rucci, P., Amendola, D., Bonizzoni, M., Cerveri, G., Colli, C., et al., 2021. Emergency psychiatric consultations during and after the COVID-19 lockdown in Italy. A multicentre study. *Front Psychiatry* 12, 697058. <https://doi.org/10.3389/fpsy.2021.697058>.
- Bao, L., Deng, W., Huang, B., Gao, H., Liu, J., Ren, L., et al., 2020. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature* 583 (7818), 830–833. <https://doi.org/10.1038/s41586-020-2312-y>.
- Bay-Richter, C., Linderholm, K.R., Lim, C.K., Samuelsson, M., Träskman-Bendz, L., Guillemin, G.J., et al., 2015. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. *Brain Behav. Immun.* 43, 110–117. <https://doi.org/10.1016/j.bbi.2014.07.012>.
- Berardelli, I., Vaia, A., Pompili, M., 2020. Thoughts of death, depression, and guilt in a healthcare worker who infected her husband with SARS-CoV-2: a case report. *CNS Neurol. Disord. Drug Targets.* <https://doi.org/10.2174/1871527319666201223155533>.
- Bergink, V., Gibney, S.M., Drexhage, H.A., 2014. Autoimmunity, inflammation, and psychosis: a search for peripheral markers. *Biol. Psychiatry* 75 (4), 324–331. <https://doi.org/10.1016/j.biopsych.2013.09.037>.
- Black, C., Miller, B.J., 2015. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biol. Psychiatry* 78 (1), 28–37. <https://doi.org/10.1016/j.biopsych.2014.10.014>.
- Boldrini, T., Girardi, P., Clerici, M., Conca, A., Creati, C., Di Cicilia, G., et al., 2021. Consequences of the COVID-19 pandemic on admissions to general hospital psychiatric wards in Italy: reduced psychiatric hospitalizations and increased suicidality. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 110, 110304. <https://doi.org/10.1016/j.pnpbp.2021.110304>.
- Boroujeni, M.E., Simani, L., Bluysen, H.A.R., Samadikhah, H.R., Zamanlui Benisi, S., Hassani, S., et al., 2021. Inflammatory response leads to neuronal death in human post-mortem cerebral cortex in patients with COVID-19. *ACS Chem. Neurosci.* 12 (12), 2143–2150. <https://doi.org/10.1021/acscchemneuro.1c00111>.
- Boulware, D.R., Pullen, M.F., Bangdiwala, A.S., Pastick, K.A., Lofgren, S.M., Okafor, E.C., et al., 2020. A randomized trial of hydroxychloroquine as postexposure prophylaxis for covid-19. *New Engl. J. Med.* 383 (6), 517–525. <https://doi.org/10.1056/NEJMoa2016638>.
- Bridges, J.P., Vladar, E.K., Huang, H., Mason, R.J., 2021. Respiratory epithelial cell responses to SARS-CoV-2 in COVID-19. *Thorax* 2021–217561. <https://doi.org/10.1136/thoraxjnl-2021-217561>.
- Brunidin, L., Bryleva, E.Y., Thirtamara Rajamani, K., 2017. Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacology* 42 (1), 271–283. <https://doi.org/10.1038/npp.2016.116>.
- Bryce, C., Grimes, Z., Pujadas, E., Ahuja, S., Beasley, M.B., Albrecht, R., et al., 2021. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Mod. Pathol.* 34 (8), 1456–1467. <https://doi.org/10.1038/s41379-021-00793-y>.
- Cabrera, B., Monroy-Jaramillo, N., Fries, G.R., Mendoza-Morales, R.C., García-Dolores, F., Mendoza-Larios, A., et al., 2019. Brain gene expression pattern of subjects with completed suicide and comorbid substance use disorder. *Mol. Neuropsychiatry* 5 (1), 60–73. <https://doi.org/10.1159/000493940>.
- Canal-Rivero, M., Catalán-Barragán, R., Rubio-García, A., Garrido-Torres, N., Crespo-Facorro, B., Ruiz-Veguilla, M., Group, I.T.P., 2021. Lower risk of SARS-CoV2 infection in individuals with severe mental disorders on antipsychotic treatment: a retrospective epidemiological study in a representative Spanish population. *Schizophr. Res.* 229, 53–54. <https://doi.org/10.1016/j.schres.2021.02.002>.
- Cantini, F., Niccoli, L., Matarrese, D., Nicastri, E., Stobbione, P., Goletti, D., 2020. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J. Infect.* 81 (2), 318–356. <https://doi.org/10.1016/j.jinf.2020.04.017>.
- Carsana, L., Sonzogni, A., Nasr, A., Rossi, R.S., Pellegrinelli, A., Zerbi, P., et al., 2020. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect. Dis.* 20 (10), 1135–1140. [https://doi.org/10.1016/S1473-3099\(20\)30434-5](https://doi.org/10.1016/S1473-3099(20)30434-5).
- Cavalcanti, A.B., Zampieri, F.G., Rosa, R.G., Azevedo, L.C.P., Veiga, V.C., Avezum, A., et al., 2020. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New Engl. J. Med.* 383 (21), 2041–2052. <https://doi.org/10.1056/NEJMoa2019014>.
- Cavalli, G., De Luca, G., Campochiaro, C., Della-Torre, E., Ripa, M., Canetti, D., et al., 2020. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheuma* 2 (6), e325–e331. [https://doi.org/10.1016/S2665-9913\(20\)30127-2](https://doi.org/10.1016/S2665-9913(20)30127-2).
- Center for Disease Control and Prevention (CDC) USA.gov, Department of Health and Human Services. Centre for Suicide Prevention, 2020. (<https://www.cdc.gov/suicide/factors/index.html>) (Accessed September 2021).
- Chacko, M., Job, A., Caston, J., George, P., Yacoub, A., Cáceda, R., 2020. COVID-19-induced psychosis and suicidal behavior: case report. *SN Compr. Clin. Med.* 1–5. <https://doi.org/10.1007/s42399-020-00530-7>.
- Chaves Filho, A.J.M., Gonçalves, F., Mottin, M., Andrade, C.H., Fonseca, S.N.S., Macedo, D.S., 2021. Repurposing of tetracyclines for COVID-19 neurological and neuropsychiatric manifestations: a valid option to control SARS-CoV-2-associated neuroinflammation? *J. Neuroimmune Pharm.* 16 (2), 213–218. <https://doi.org/10.1007/s11481-021-09986-3>.

- Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., et al., 2020. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Invest.* 130 (5), 2620–2629. <https://doi.org/10.1172/JCI137244>.
- Chen, L.Y.C., Hoiland, R.L., Stukas, S., Wellington, C.L., Sekhon, M.S., 2021. Assessing the importance of interleukin-6 in COVID-19. *Lancet Respir. Med.* 9 (2) [https://doi.org/10.1016/S2213-2600\(20\)30600-7](https://doi.org/10.1016/S2213-2600(20)30600-7).
- Conti, P., Caraffa, A., Tete, G., Gallenga, C.E., Ross, R., Kritas, S.K., et al., 2020. Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19. *J. Biol. Regul. Homeost. Agents* 34 (5), 1629–1632. <https://doi.org/10.23812/20-2EDIT>.
- Convertino, I., Tuccori, M., Ferraro, S., Valdiserra, G., Cappello, E., Focosi, D., Blandizzi, C., 2020. Exploring pharmacological approaches for managing cytokine storm associated with pneumonia and acute respiratory distress syndrome in COVID-19 patients, 331–331 *Crit. Care* 24 (1). <https://doi.org/10.1186/s13054-020-03020-3>.
- Coryell, W., Wilcox, H., Evans, S.J., Pandey, G.N., Jones-Brandt, L., Dickerson, F., Yolken, R., 2018. Aggression, impulsivity and inflammatory markers as risk factors for suicidal behavior. *J. Psychiatr. Res.* 106, 38–42. <https://doi.org/10.1016/j.jpsychires.2018.09.004>.
- Costantini, L., Pasquarella, C., Odone, A., Colucci, M.E., Costanza, A., Serafini, G., Aguglia, A., Belvederi Murri, M., Brakoulias, V., Amore, M., Ghaemi, S.N., Amerio, A., 2021. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): a systematic review. *J. Affect Disord.* 279, 473–483. <https://doi.org/10.1016/j.jad.2020.09.131>.
- Costanza, A., D'Orta, I., Perroud, N., Burkhardt, S., Malafosse, A., Mangin, P., La Harpe, R., 2013. Neurobiology of suicide: do biomarkers exist? *Int. J. Leg. Med.* 128 (1), 73–82. <https://doi.org/10.1007/s00414-013-0835-6>.
- Costanza, A., Baertschi, M., Weber, K., Canuto, A., 2015. [Neurological diseases and suicide: from neurobiology to hopelessness]. *Rev. Med. Suisse* 11 (461), 402–405.
- Costanza, A., Di Marco, S., Burroni, M., Corasaniti, F., Santinon, P., Prelati, M., et al., 2020a. Meaning in life and demoralization: a mental-health reading perspective of suicidality in the time of COVID-19. *Acta Biomed.* 91 (4), e2020163 <https://doi.org/10.23750/abm.v91i4.10515>.
- Costanza, A., Amerio, A., Aguglia, A., Escelsior, A., Serafini, G., Berardelli, I., et al., 2020b. When sick brain and hopelessness meet: some aspects of suicidality in the neurological patient. *CNS Neurol. Disord. Drug Targets* 19 (4), 257–263. <https://doi.org/10.2174/1871527319666200611130804>.
- Costanza, A., Amerio, A., Aguglia, A., Serafini, G., Amore, M., Macchiarulo, et al., 2021a. From “The Interpersonal Theory of Suicide” to “The Interpersonal Trust”: an unexpected and effective resource to mitigate economic crisis-related suicide risk in times of Covid-19? *Acta Biomed.* 92 (S6), e2021417 <https://doi.org/10.23750/abm.v92iS6.12249>.
- Costanza, A., Rothen, S., Achab, S., Thorens, G., Baertschi, M., Weber, K., et al., 2021b. Impulsivity and impulsivity-related endophenotypes in suicidal patients with substance use disorders: an exploratory study. *Int. J. Ment. Health Addict.* 19 (5), 1729–1744. <https://doi.org/10.1007/s11469-020-00259-3>.
- Costanza, A., Placenti, V., Amerio, A., Aguglia, A., Serafini, G., Amore, M., Macchiarulo, E., Branca, F., Merli, R., Bondolfi, G., Nguyen, K.D., 2021c. Chloroquine/Hydroxychloroquine Use and Suicide Risk: Hypotheses for Confluent Etiopathogenetic Mechanisms? *Behav. Sci.* 11 (11), 154. <https://doi.org/10.3390/bs11110154>.
- Coughlin, S.S., Sher, L., 2013. Suicidal behavior and neurological illnesses. *J. Depress Anxiety Suppl* 9 (1), 12443. <https://doi.org/10.4172/2167-1044.S9-001>.
- Courtet, P., Giner, L., Seneque, M., Guillaume, S., Olie, E., Ducasse, D., 2015. Neuroinflammation in suicide: toward a comprehensive model. *World J. Biol. Psychiatry* 17 (8), 564–586. <https://doi.org/10.3109/15622975.2015.1054879>.
- Crespo-Facorro, B., Ruiz-Veguilla, M., Vázquez-Bourgon, J., Sánchez-Hidalgo, A.C., Garrido-Torres, N., Cisneros, J.M., et al., 2021. Aripiprazole as a candidate treatment of COVID-19 identified through genomic analysis. *Front. Pharm.* 12 <https://doi.org/10.3389/fphar.2021.646701>.
- DeVylder, J., Zhou, S., Oh, H., 2021. Suicide attempts among college students hospitalized for COVID-19. *J. Affect Disord.* 294, 241–244. <https://doi.org/10.1016/j.jad.2021.07.058>.
- Diaz, A., Taub, C.J., Lippman, M.E., Antoni, M.H., Blomberg, B.B., 2021. Effects of brief stress management interventions on distress and leukocyte nuclear factor kappa B expression during primary treatment for breast cancer: a randomized trial. *Psychoneuroendocrinology* 126, 105163. <https://doi.org/10.1016/j.psyneuen.2021.105163>.
- Dube, J.P., Smith, M.M., Sherry, S.B., Hewitt, P.L., Stewart, S.H., 2021. Suicide behaviors during the COVID-19 pandemic: a meta-analysis of 54 studies. *Psychiatry Res* 301, 113998. <https://doi.org/10.1016/j.psychres.2021.113998>.
- Ducasse, D., Olié, E., Guillaume, S., Artéro, S., Courtet, P., 2015. A meta-analysis of cytokines in suicidal behavior. *Brain Behav. Immun.* 46, 203–211. <https://doi.org/10.1016/j.bbi.2015.02.004>.
- Dufort, E.M., Koumans, E.H., Chow, E.J., Rosenthal, E.M., Muse, A., Rowlands, J., et al., 2020. Multisystem Inflammatory Syndrome in Children in New York State. *New Engl. J. Med.* 383 (4), 347–358. <https://doi.org/10.1056/NEJMoa2021756>.
- Eskandary, F., Dürr, M., Budde, K., Doberer, K., Reindl-Schwaighofer, R., Waiser, J., et al., 2019. Clazakizumab in late antibody-mediated rejection: study protocol of a randomized controlled pilot trial, 37–37 *Trials* 20 (1). <https://doi.org/10.1186/s13063-018-3158-6>.
- Feldmann, M., Maini, R.N., Woody, J.N., Holgate, S.T., Winter, G., Rowland, M., et al., 2020. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* 395 (10234), 1407–1409. [https://doi.org/10.1016/S0140-6736\(20\)30858-8](https://doi.org/10.1016/S0140-6736(20)30858-8).
- Feldstein, L.R., Rose, E.B., Horwitz, S.M., Collins, J.P., Newhams, M.M., Son, M.B.F., et al., 2020. Multisystem inflammatory syndrome in U.S. children and adolescents. *N. Engl. J. Med.* 383 (4), 334–346. <https://doi.org/10.1056/NEJMoa2021680>.
- Fiorillo, A., Gorwood, P., 2020. The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. *Eur. Psychiatry* 63 (1), e32. <https://doi.org/10.1192/j.eurpsy.2020.35>.
- Fox, S.E., Akmatbekov, A., Harbert, J.L., Li, G., Quincy Brown, J., Vander Heide, R.S., 2020. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir. Med.* 8 (7), 681–686. [https://doi.org/10.1016/S2213-2600\(20\)30243-5](https://doi.org/10.1016/S2213-2600(20)30243-5).
- Frieri, M., 2015. Mast cell activation syndrome. *Clin. Rev. Allergy Immunol.* 54 (3), 353–365. <https://doi.org/10.1007/s12016-015-8487-6>.
- Gabbay, V., Klein, R.G., Guttman, L.E., Babb, J.S., Alonso, C.M., Nishawala, M., et al., 2009. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. *J. Child Adolesc. Psychopharmacol.* 19 (4), 423–430. <https://doi.org/10.1089/cap.2008.0140>.
- Gança, L., Oquendo, M.A., Tyrka, A.R., Cisneros-Trujillo, S., Mann, J.J., Sublette, M.E., 2016. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology* 63, 296–310. <https://doi.org/10.1016/j.psyneuen.2015.10.008>.
- García-Beltrán, W.F., Lam, E.C., Astudillo, M.G., Yang, D., Miller, T.E., Feldman, J., et al., 2021. COVID-19-neutralizing antibodies predict disease severity and survival. *e111 Cell* 184 (2), 476–488. <https://doi.org/10.1016/j.cell.2020.12.015>.
- Gebremeskel, S., Schanin, J., Coyle, K.M., Butuci, M., Luu, T., Brock, E.C., et al., 2021. Mast cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-siglec-8 antibody. *Front. Immunol.* 12 <https://doi.org/10.3389/fimmu.2021.650331>.
- Georgin-Lavialle, S., Gaillard, R., Moura, D., Hermine, O., 2016. Mastocytosis in adulthood and neuropsychiatric disorders. *Transl. Res.* 174 (77–85), e71 <https://doi.org/10.1016/j.trsl.2016.03.013>.
- Georgin-Lavialle, S., Moura, D.S., Salvador, A., Chauvet-Gelinier, J.C., Launay, J.M., Damaj, G., et al., 2016. Mast cells' involvement in inflammation pathways linked to depression: evidence in mastocytosis. *Mol. Psychiatry* 21 (11), 1511–1516. <https://doi.org/10.1038/mp.2015.216>.
- Giamarellos-Bourboulis, E.J., Netea, M.G., Rovina, N., Akinosoglou, K., Antoniadou, A., Antonakos, N., et al., 2020. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 27 (6), 992–1000. <https://doi.org/10.1016/j.chom.2020.04.009>.
- Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., et al., 2010. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 330 (6005), 841–845. <https://doi.org/10.1126/science.1194637>.
- Goyal, K., Chauhan, P., Chhikara, K., Gupta, P., Singh, M.P., 2020. Fear of COVID 2019: first suicidal case in India! *Asian J. Psychiatr.* 49, 101989 <https://doi.org/10.1016/j.ajp.2020.101989>.
- Grant, R.A., Morales-Nebreda, L., Markov, N.S., Swaminathan, S., Querrey, M., Guzman, E.R., et al., 2021. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature* 590 (7847), 635–641. <https://doi.org/10.1038/s41586-020-03148-w>.
- Grassi-Oliveira, R., Brieztke, E., Teixeira, A., Pezzi, J.C., Zanini, M., Lopes, R.P., Bauer, M.E., 2012. Peripheral chemokine levels in women with recurrent major depression with suicidal ideation. *Rev. Bras. De Psiquiatr.* 34 (1), 71–75. [https://doi.org/10.1016/s1516-4446\(12\)70013-2](https://doi.org/10.1016/s1516-4446(12)70013-2).
- Grunebaum, M.F., Ramsay, S.R., Galfalvy, H.C., Ellis, S.P., Burke, A.K., Sher, L., et al., 2006. Correlates of suicide attempt history in bipolar disorder: a stress-diathesis perspective. *Bipolar Disord.* 8 (5p2), 551–557. <https://doi.org/10.1111/j.1399-5618.2006.00304.x>.
- Gunnell, D., Appleby, L., Arensman, E., Hawton, K., John, A., Kapur, N., et al., 2020. Suicide risk and prevention during the COVID-19 pandemic. *Lancet Psychiatry* 7 (6), 468–471. [https://doi.org/10.1016/S2215-0366\(20\)30171-1](https://doi.org/10.1016/S2215-0366(20)30171-1).
- Gustine, J.N., Jones, D., 2021. Immunopathology of Hyperinflammation in COVID-19. *Am. J. Pathol.* 191 (1), 4–17. <https://doi.org/10.1016/j.ajpath.2020.08.009>.
- Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Smith, N., et al., 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 369 (6504), 718–724. <https://doi.org/10.1126/science.abc6027>.
- Hafezi, B., Chan, L., Knapp, J.P., Karimi, N., Alizadeh, K., Mehrani, Y., et al., 2021. Cytokine storm syndrome in SARS-CoV-2 infections: a functional role of mast cells. *Cells* 10 (7), 1761. <https://doi.org/10.3390/cells10071761>.
- Hamm, B.S., Rosenthal, L.J., 2020. Psychiatric aspects of chloroquine and hydroxychloroquine treatment in the wake of Coronavirus Disease-2019: psychopharmacological interactions and neuropsychiatric sequelae. *Psychosomatics* 61 (6), 597–606. <https://doi.org/10.1016/j.psym.2020.06.022>.
- Hawton, K., van Heeringen, K., 2009. Suicide. *Lancet* 373 (9672), 1372–1381. [https://doi.org/10.1016/s0140-6736\(09\)60372-x](https://doi.org/10.1016/s0140-6736(09)60372-x).
- Hendrikus, E., van Bergeijk, D.A., Oosting, R.S., Redegeld, F.A., 2017. 'Corrigendum to: "Mast cells in neuroinflammation and brain disorders"'. *Neurosci. Biobehav. Rev.* 83, 774. <https://doi.org/10.1016/j.neubiorev.2017.10.030>.
- Hensley, M.K., Markantone, D., Prescott, H.C., 2021. Neurologic manifestations and complications of COVID-19. *Ann. Rev. Med.* 73 (1). <https://doi.org/10.1146/annurev-med-042320-010427>.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395 (10223), 497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- Hudzik, T.J., Marek, G.J., 2014. Neurological disease and suicidal behavior. In: Cannon, K.E., Hudzik, T.J. (Eds.), *Suicide: Phenomenology and Neurobiology*. Springer International Publishing, Cham, Switzerland, pp. 155–166.

- Huet, T., Beaussier, H., Voisin, O., Jouvesshomme, S., Dauriat, G., Lazareth, I., et al., 2020. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheuma* 2 (7), e393–e400. [https://doi.org/10.1016/S2665-9913\(20\)30164-8](https://doi.org/10.1016/S2665-9913(20)30164-8).
- Hussell, T., Bell, T.J., 2014. Alveolar macrophages: plasticity in a tissue-specific context. *Nat. Rev. Neurol.* 14 (2), 81–93. <https://doi.org/10.1038/nri3600>.
- John, A., Eyles, E., Webb, R.T., Okolie, C., Schmidt, L., Arensman, E., et al., 2020. The impact of the COVID-19 pandemic on self-harm and suicidal behaviour: update of living systematic review. *F1000Res* 9, 1097. <https://doi.org/10.12688/f1000research.25522.2>.
- Kahil, K., Cheaito, M.A., El Hayek, R., Nofal, M., El Halabi, S., Kudva, K.G., et al., 2021. Suicide during COVID-19 and other major international respiratory outbreaks: a systematic review. *Asian J. Psychiatr.* 56, 102509. <https://doi.org/10.1016/j.ajp.2020.102509>.
- Kaliyurthi, S., Selvaraj, G., Selvaraj, C., Singh, S.K., Wei, D.-Q., Peshherbe, G.H., 2021. Structure-based virtual screening reveals ibrutinib and zanubrutinib as potential repurposed drugs against COVID-19. *Int. J. Mol. Sci.* 22 (13), 7071. <https://doi.org/10.3390/ijms22137071>.
- Kanberg, N., Simrén, J., Edén, A., Andersson, L.-M., Nilsson, S., Ashton, N.J., et al., 2021. Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine* 70. <https://doi.org/10.1016/j.ebiom.2021.103512>.
- Kapellos, T.S., Bonaguro, L., Gemünd, I., Reusch, N., Saglam, A., Hinkley, E.R., Schultze, J.L., 2019. Human monocyte subsets and phenotypes in major chronic inflammatory diseases. *Front Immunol.* 10. <https://doi.org/10.3389/fimmu.2019.02035>.
- Kazama, I., 2020. Stabilizing mast cells by commonly used drugs: a novel therapeutic target to relieve post-COVID syndrome? *Drug Discov. Ther.* 14 (5), 259–261. <https://doi.org/10.5582/ddt.2020.03095>.
- Keaton, S.A., Madaj, Z.B., Heilman, P., Smart, L., Grit, J., Gibbons, R., et al., 2019. An inflammatory profile linked to increased suicide risk. *J. Affect Disord.* 247, 57–65. <https://doi.org/10.1016/j.jad.2018.12.100>.
- Kempuraj, D., Selvakumar, G.P., Ahmed, M.E., Raikwar, S.P., Thangavel, R., Khan, A., et al., 2020a. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. *Neuroscientist* 26 (5–6), 402–414. <https://doi.org/10.1177/1073858420941476>.
- Kempuraj, D., Thangavel, R., Kempuraj, D.D., Ahmed, M.E., Selvakumar, G.P., Raikwar, S.P., et al., 2020b. Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. *BioFactors* 47 (2), 190–197. <https://doi.org/10.1002/biof.1687>.
- Kim, Y.-K., Lee, S.-W., Kim, S.-H., Shim, S.-H., Han, S.-W., Choi, S.-H., Lee, B.-H., 2008. Differences in cytokines between non-suicidal patients and suicidal patients in major depression. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 32 (2), 356–361. <https://doi.org/10.1016/j.pnpbp.2007.08.041>.
- Kim, Y.-K., Hong, J.-P., Hwang, J.-A., Lee, H.-J., Yoon, H.-K., Lee, B.-H., 2013. TNF-alpha -308G>a polymorphism is associated with suicide attempts in major depressive disorder. *J. Affect Disord.* 150 (2), 668–672. <https://doi.org/10.1016/j.jad.2013.03.019>.
- Knowles, E.E.M., Curran, J.E., Göring, H.H.H., Mathias, S.R., Mollon, J., Rodrigue, A., et al., 2019. Family-based analyses reveal novel genetic overlap between cytokine interleukin-8 and risk for suicide attempt. *Brain Behav. Immun.* 80, 292–299. <https://doi.org/10.1016/j.bbi.2019.04.004>.
- Lee, M.-H., Perl, D.P., Nair, G., Li, W., Maric, D., Murray, H., et al., 2021. Microvascular injury in the brains of patients with Covid-19. *New Engl. J. Med.* 384 (5), 481–483. <https://doi.org/10.1056/NEJMc2033669>.
- Lehrer, S., Rheinstein, P.H., 2019. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce suicidal ideation and depression. *Disco Med* 28 (154), 205–212.
- Leisman, D.E., Ronner, L., Pinotti, R., Taylor, M.D., Sinha, P., Calfee, C.S., et al., 2021. Assessing the importance of interleukin-6 in COVID-19 - Authors' reply. *Lancet Respir. Med.* 9 (2), e14–e15. [https://doi.org/10.1016/S2213-2600\(20\)30603-2](https://doi.org/10.1016/S2213-2600(20)30603-2).
- Leske, S., Kolves, K., Crompton, D., Arensman, E., de Leo, D., 2021. Real-time suicide mortality data from police reports in Queensland, Australia, during the COVID-19 pandemic: an interrupted time-series analysis. *Lancet Psychiatry* 8 (1), 58–63. [https://doi.org/10.1016/S2215-0366\(20\)30435-1](https://doi.org/10.1016/S2215-0366(20)30435-1).
- Liao, M., Liu, Y., Yuan, J., Wen, Y., Xu, G., Zhao, J., et al., 2020. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat. Med.* 26 (6), 842–844. <https://doi.org/10.1038/s41591-020-0901-9>.
- Lindqvist, D., Janelidze, S., Hagell, P., Erhardt, S., Samuelsson, M., Minthon, L., et al., 2009. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol. Psychiatry* 66 (3), 287–292. <https://doi.org/10.1016/j.biopsych.2009.01.030>.
- Linnerbauer, M., Wheeler, M.A., Quintana, F.J., 2020. Astrocyte crosstalk in CNS inflammation. *Neuron* 108 (4), 608–622. <https://doi.org/10.1016/j.neuron.2020.08.012>.
- Liu, Y., Cao, L., Li, X., Jia, Y., Xia, H., 2020. Awareness of mental health problems in patients with coronavirus disease 19 (COVID-19): a lesson from an adult man attempting suicide. *Asian J. Psychiatr.* 51, 102106. <https://doi.org/10.1016/j.ajp.2020.102106>.
- Lucas, C., Wong, P., Klein, J., Castro, T.B.R., Silva, J., Sundaram, M., et al., 2020. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 584 (7821), 463–469. <https://doi.org/10.1038/s41586-020-2588-y>.
- Maes, M., Van Der Planken, M., Stevens, W.J., Peeters, D., DeClerck, L.S., Bridts, C.H., et al., 1992. Leukocytosis, monocytosis and neutrophilia: hallmarks of severe depression. *J. Psychiatr. Res* 26 (2), 125–134. [https://doi.org/10.1016/0022-3956\(92\)90004-8](https://doi.org/10.1016/0022-3956(92)90004-8).
- Majumder, J., Minko, T., 2021. Recent developments on therapeutic and diagnostic approaches for COVID-19. *AAPS J.* 23 (1). <https://doi.org/10.1208/s12248-020-00532-2>.
- Mamun, M.A., Griffiths, M.D., 2020. First COVID-19 suicide case in Bangladesh due to fear of COVID-19 and xenophobia: possible suicide prevention strategies. *Asian J. Psychiatr.* 51, 102073. <https://doi.org/10.1016/j.ajp.2020.102073>.
- Manganelli, F., Vargas, M., Iovino, A., Iacovazzo, C., Santoro, L., Servillo, G., 2020. Brainstem involvement and respiratory failure in COVID-19. *Neurol. Sci.* 41 (7), 1663–1665. <https://doi.org/10.1007/s10072-020-04487-2>.
- Mann, J.J., Currier, D.M., 2010. Stress, genetics and epigenetic effects on the neurobiology of suicidal behavior and depression. *Eur. Psychiatry. J. Assoc. Eur. Psychiatr.* 25 (5), 268–271. <https://doi.org/10.1016/j.eurpsy.2010.01.009>.
- Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J.P., Schröder, A.S., Edler, C., et al., 2020. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol.* 19 (11), 919–929. [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2).
- Mazza, M.G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bolletini, I., et al., 2020. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav. Immun.* 89, 594–600. <https://doi.org/10.1016/j.bbi.2020.07.037>.
- McIntyre, A., Tong, K., McMahon, E., Doherty, A.M., 2021. COVID-19 and its effect on emergency presentations to a tertiary hospital with self-harm in Ireland. *Ir. J. Psychol. Med.* 38 (2), 116–122. <https://doi.org/10.1017/ijpm.2020.116>.
- Meira, F., Albiach, L., Carbonell, C., Martín-Oterio, J.A., Martín-Ordiales, M., Linares, L., et al., 2021. Experience with the use of siltuximab in patients with SARS-CoV-2 infection. *Rev. Esp. Quim.* 34 (4), 337–341. <https://doi.org/10.37201/req/045.2021>.
- Miná, V.A.L., Lacerda-Pinheiro, S.F., Maia, L.C., Pinheiro, R.F.F., Meireles, C.B., de Souza, S.I.R., et al., 2015. The influence of inflammatory cytokines in physiopathology of suicidal behavior. *J. Affect Disord.* 172, 219–230. <https://doi.org/10.1016/j.jad.2014.09.057>.
- Molderings, G.J., Meis, K., Kolck, U.W., Homann, J., Frieling, T., 2010. Comparative analysis of mutation of tyrosine kinase kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 62 (11–12), 721–727. <https://doi.org/10.1007/s00251-010-0474-8>.
- Mondal, R., Ganguly, U., Deb, S., Shome, G., Pramanik, S., Bandyopadhyay, D., Lahiri, D., 2021. Meningoencephalitis associated with COVID-19: a systematic review. *J. Neurovirol.* 27 (1), 12–25. <https://doi.org/10.1007/s13365-020-00923-3>.
- Montalbani, B., Bargagna, P., Mastrangelo, M., Sarubbi, S., Imbastro, B., De Luca, G.P., et al., 2021. The COVID-19 outbreak and subjects with mental disorders who presented to an Italian psychiatric emergency department. *J. Nerv. Ment. Dis.* 209 (4), 246–250. <https://doi.org/10.1097/NMD.0000000000001289>.
- Motta Junior, Jd.S., Miggiolaro, A.F.R.D.S., Nagashima, S., de Paula, C.B.V., Baena, C.P., Scharfstein, J., de Noronha, L., 2020. Mast cells in alveolar septa of COVID-19 patients: a pathogenic pathway that may link interstitial edema to immunothrombosis. *Front Immunol.* 11. <https://doi.org/10.3389/fimmu.2020.574862>.
- Moura, D.S., Sultan, S., Georjina-Lavialle, S., Pillet, N., Montestruc, F., Gineste, P., 2011. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. *PLoS One* 6 (10). <https://doi.org/10.1371/journal.pone.0026375>.
- Moura, D.S., Sultan, S., Georjina-Lavialle, S., Barete, S., Lortholary, O., Gaillard, R., Hermine, O., 2012. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. *PLoS One* 7 (6). <https://doi.org/10.1371/journal.pone.0039468>.
- Moutsopoulos, H.M., Zampeli, E., Vlachoyiannopoulos, P.G., 2018. Medications, therapeutic modalities, and regimens used in the management of rheumatic diseases. In: Moutsopoulos, H.M., Zampeli, E., Vlachoyiannopoulos, P.G. (Eds.), *Rheumatology in Questions*. Springer International Publishing, Cham, Switzerland, pp. 153–175.
- Na, P., Tsai, J., Harpaz-Rotem, I., Pietrzak, R., 2021. Mental health and suicidal ideation in US military veterans with histories of COVID-19 infection. *BMJ Mil. Health.* <https://doi.org/10.1136/bmjilitary-2021-001846>.
- Naliballe, K., Reddy Onteddu, S., Sharma, R., Dandu, V., Brown, A., Jasti, M., et al., 2020. Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav. Immun.* 88, 71–74. <https://doi.org/10.1016/j.bbi.2020.06.020>.
- Nemirovsky, A., Ilan, K., Lerner, L., Cohen-Lavi, L., Schwartz, D., Goren, G., et al., 2021. Brain-immune axis regulation is responsive to cognitive behavioral therapy and mindfulness intervention: Observations from a randomized controlled trial in patients with Crohn's disease. *Brain Behav. Immun. Health* 23. <https://doi.org/10.1016/j.bbih.2021.100407>.
- Ngo, B., Lapp, S.A., Siegel, B., Patel, V., Hussaini, L., Bora, S., et al., 2021. Cerebrospinal fluid cytokine, chemokine, and SARS-CoV-2 antibody profiles in children with neuropsychiatric symptoms associated with COVID-19. *Mult. Scler. Relat. Disord.* 55. <https://doi.org/10.1016/j.msard.2021.103169>.
- Niederkrotenthaler, T., Gunnell, D., Arensman, E., Pirkis, J., Appleby, L., Hawton, K., et al., 2020. Suicide research, prevention, and COVID-19. *Crisis* 41 (5), 321–330. <https://doi.org/10.1027/0227-5910/a000731>.
- Nowak, W., Grendas, L.N., Sanmarco, L.M., Estecho, I.G., Arena, Á.R., Eberhardt, N., et al., 2019. Pro-inflammatory monocyte profile in patients with major depressive disorder and suicide behaviour and how ketamine induces anti-inflammatory M2 macrophages by NMDAR and mTOR. *EBioMedicine* 50, 290–305. <https://doi.org/10.1016/j.ebiom.2019.10.063>.
- Ong, W.-Y., Go, M.-L., Wang, D.-Y., Cheah, I.K.M., Halliwell, B., 2021. Effects of antimalarial drugs on neuroinflammation-potential use for treatment of COVID-19-related neurologic complications. *Mol. Neurobiol.* 58 (1), 106–117. <https://doi.org/10.1007/s12035-020-02093-z>.

- Pandey, G.N., Rizavi, H.S., Zhang, H., Bhaumik, R., Ren, X., 2018. Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide. *J. Psychiatry Neurosci.* 43 (6), 376–385. <https://doi.org/10.1503/jpn.170192>.
- Patterson, B.K., Seethamraju, H., Dhody, K., Corley, M.J., Kazempour, K., Lalezari, J., et al., 2020. Disruption of the CCL5/RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. *medRxiv*. <https://doi.org/10.1101/2020.05.02.20084673>.
- Pellegrini, L., Albecka, A., Mallery, D.L., Kellner, M.J., Paul, D., Carter, A.P., et al., 2020. SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. *Cell Stem Cell* 27 (6), 951–961. <https://doi.org/10.1016/j.stem.2020.10.001>.
- Phiri, P., Ramakrishnan, R., Rathod, S., Elliot, K., Thayanandan, T., Sandle, N., et al., 2021. An evaluation of the mental health impact of SARS-CoV-2 on patients, general public and healthcare professionals: a systematic review and meta-analysis. *EclinicalMedicine* 34, 100806. <https://doi.org/10.1016/j.eclinm.2021.100806>.
- Pirkis, J., John, A., Shin, S., DelPozo-Banos, M., Arya, V., Analuisa-Aguilar, P., et al., 2021. Suicide trends in the early months of the COVID-19 pandemic: an interrupted time-series analysis of preliminary data from 21 countries. *Lancet Psychiatry* 8 (7), 579–588. [https://doi.org/10.1016/S2215-0366\(21\)00091-2](https://doi.org/10.1016/S2215-0366(21)00091-2).
- Pirnia, B., Dezhakam, H., Pirnia, K., Malekanmehr, P., Rezaeian, M., 2020. Grief of COVID-19 is a mental contagion, first family suicide in Iran. *Asian J. Psychiatr.* 54, 102340. <https://doi.org/10.1016/j.ajp.2020.102340>.
- Poloni, T.E., Medici, V., Moretti, M., Visonà, S.D., Cirrincione, A., Carlos, A.F., et al., 2021. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. *Brain Pathol.* 31 (5) <https://doi.org/10.1111/bpa.12997>.
- Pompili, M., 2021. Can we expect a rise in suicide rates after the Covid-19 pandemic outbreak? *Eur. Neuropsychopharmacol.* 52, 1–2. <https://doi.org/10.1016/j.euroneuro.2021.05.011>.
- Pompili, M., Gentile, G., Scasellati, C., Bonvicini, C., Innamorati, M., Erbuto, D., et al., 2017. Genetic association analysis of serotonin and signal transduction pathways in suicide attempters from an Italian sample of psychiatric patients. *Neurosci. Lett.* 656, 94–102. <https://doi.org/10.1016/j.neulet.2017.07.020>.
- Postolache, T.T., Benros, M.E., Brenner, L.A., 2021. Targetable biological mechanisms implicated in emergent psychiatric conditions associated with SARS-CoV-2 infection. *JAMA Psychiatry* 78 (4), 353. <https://doi.org/10.1001/jamapsychiatry.2020.2795>.
- Reger, M.A., Stanley, I.H., Joiner, T.E., 2020. Suicide mortality and coronavirus disease 2019—a perfect storm? *JAMA Psychiatry* 77 (11), 1093–1094. <https://doi.org/10.1001/jamapsychiatry.2020.1060>.
- Reichard, R.R., Kashani, K.B., Boire, N.A., Constantopoulos, E., Guo, Y., Lucchinetti, C.F., 2020. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol.* 140 (1), 1–6. <https://doi.org/10.1007/s00401-020-02166-2>.
- Ribeiro Dos Santos Miggiolaro, A.F., da Silva Motta Junior, J., Busatta Vaz de Paula, C., Nagashima, S., Alessandra Scaranello Malaquias, M., Baena Carstens, L., et al., 2020. Covid-19 cytokine storm in pulmonary tissue: anatomopathological and immunohistochemical findings. *Respir. Med. Case Rep.* 31 <https://doi.org/10.1016/j.rmcr.2020.101292>.
- Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., et al., 2020. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 395 (10223), e30–e31. [https://doi.org/10.1016/S0140-6736\(20\)30304-4](https://doi.org/10.1016/S0140-6736(20)30304-4).
- Robinson, P.C., Richards, D., Tanner, H.L., Feldmann, M., 2020. Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. *Lancet Rheuma* 2 (11), e653–e655. [https://doi.org/10.1016/S2665-9913\(20\)30309-X](https://doi.org/10.1016/S2665-9913(20)30309-X).
- Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., et al., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 7 (7), 611–627. [https://doi.org/10.1016/S2215-0366\(20\)30203-0](https://doi.org/10.1016/S2215-0366(20)30203-0).
- Romero-Sánchez, C.M., Díaz-Maroto, I., Fernández-Díaz, E., Sánchez-Larsen, Á., Layos-Romero, A., García-García, J., et al., 2020. Neurologic manifestations in hospitalized patients with COVID-19: The ALBA COVID registry. *Neurology* 95 (8), e1060–e1070. <https://doi.org/10.1212/WNL.0000000000009937>.
- Sánchez-Cerrillo, I., Landete, P., Aldave, B., Sánchez-Alonso, S., Sánchez-Azofra, A., Marcos-Jiménez, A., et al., 2020. COVID-19 severity associates with pulmonary redistribution of CD1c+ DCs and inflammatory transitional and nonclassical monocytes. *J. Clin. Invest.* 130 (12), 6290–6300. <https://doi.org/10.1172/JCI140335>.
- Schlicht, K., Büttner, A., Siedler, F., Scheffer, B., Zill, P., Eisenmenger, W., et al., 2007. Comparative proteomic analysis with postmortem prefrontal cortex tissues of suicide victims versus controls. *J. Psychiatr. Res.* 41 (6), 493–501. <https://doi.org/10.1016/j.jpsychires.2006.04.006>.
- Schneider, T.P., Trencavska, I., Rosoklija, G., Stankov, A., Mann, J.J., Smiley, J., Dwork, A.J., 2014. Microglia of prefrontal white matter in suicide. *J. Neuropathol. Exp. Neurol.* 73 (9), 880–890. <https://doi.org/10.1097/NEN.000000000000107>.
- Schulte-Schrepping, J., Reusch, N., Paclik, D., Bassler, K., Schlickeiser, S., Zhang, B., et al., 2020. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell* 182 (6), 1419–1440. <https://doi.org/10.1016/j.cell.2020.08.001>.
- Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C.S.C., de Boer, H.H., et al., 2020. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 1 (7), e290–e299. [https://doi.org/10.1016/S2666-5247\(20\)30144-0](https://doi.org/10.1016/S2666-5247(20)30144-0).
- Schwabenland, M., Salić, H., Tanevski, J., Killmer, S., Lago, M.S., Schlaak, A.E., et al., 2021. Deep spatial profiling of human COVID-19 brains reveals neuroinflammation with distinct microanatomical microglia-T-cell interactions. *Immunity* 54 (7), 1594–1610. <https://doi.org/10.1016/j.immuni.2021.06.002>.
- Sciascia, S., Apra, F., Baffa, A., Baldovino, S., Boaro, D., Boero, R., et al., 2020. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin. Exp. Rheuma* 38 (3), 529–532.
- Serafini, G., Pompili, M., Elena Seretti, M., Stefani, H., Palermo, M., Coryell, W., Girardi, P., 2013. The role of inflammatory cytokines in suicidal behavior: a systematic review. *Eur. Neuropsychopharmacol.* 23 (12), 1672–1686. <https://doi.org/10.1016/j.euroneuro.2013.06.002>.
- Serafini, G., Parisi, V.M., Aguglia, A., Amerio, A., Sampogna, G., Fiorillo, A., Pompili, M., et al., 2020. A specific inflammatory profile underlying suicide risk? Systematic review of the main literature findings. *Int. J. Environ. Res. Public Health* 17 (7), 2393. <https://doi.org/10.3390/ijerph17072393>.
- Sher, L., 2020a. The impact of the COVID-19 pandemic on suicide rates. *QJM* 113 (10), 707–712. <https://doi.org/10.1093/qjmed/hcaa202>.
- Sher, L., 2020b. Are COVID-19 survivors at increased risk for suicide? *Acta Neuropsychiatr.* 32 (5), 270. <https://doi.org/10.1017/neu.2020.21>.
- Sher, L., 2021. Post-COVID syndrome and suicide risk. *QJM* 114 (2), 95–98. <https://doi.org/10.1093/qjmed/hcab007>.
- Shields, G.S., Spahr, C.M., Slavich, G.M., 2020. Psychosocial interventions and immune system function: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 77, 1031–1043. <https://doi.org/10.1001/jamapsychiatry.2020.0431>.
- Sieper, J., Braun, J., Kay, J., Badalamenti, S., Radin, A.R., Jiao, L., et al., 2015. Sarilumab for the treatment of ankylosing spondylitis: results of a Phase II, randomised, double-blind, placebo-controlled study (ALIGN). *Ann. Rheum. Dis.* 74 (6), 1051–1057. <https://doi.org/10.1136/annrheumdis-2013-204963>.
- Soria-Castro, R., Meneses-Preza, Y.G., Rodríguez-López, G.M., Romero-Ramírez, S., Sosa-Hernández, V.A., Cervantes-Díaz, R., et al., 2021. Severe COVID-19 is marked by dysregulated serum levels of carboxypeptidase A3 and serotonin. *J. Leukoc. Biol.* 110 (3), 425–431. <https://doi.org/10.1002/JLB.4HI0221-087R>.
- Stack, M., Sacco, K., Castagnoli, R., Livinski, A.A., Notarangelo, L.D., Lionakis, M.S., 2021. BTK inhibitors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a systematic review. *Clin. Immunol.* 230 <https://doi.org/10.1016/j.clim.2021.108816>.
- Steardo Jr., L., Steardo, L., Verkhatsky, A., 2020. Psychiatric face of COVID-19. *Transl. Psychiatry* 10 (1). <https://doi.org/10.1038/s41398-020-00949-5>.
- Steiner, J., Bielau, H., Brisch, R., Danos, P., Ullrich, O., Mawrin, C., et al., 2008. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. *J. Psychiatr. Res.* 42 (2), 151–157. <https://doi.org/10.1016/j.jpsychires.2006.10.013>.
- Sublette, M.E., Galfalvy, H.C., Fuchs, D., Lapidus, M., Grunebaum, M.F., Oquendo, M.A., et al., 2011. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. *Brain Behav. Immun.* 25 (6), 1272–1278. <https://doi.org/10.1016/j.bbi.2011.05.002>.
- Sundquist, K., Memon, A.A., Palmér, K., Sundquist, J., Wang, X., 2021. Inflammatory proteins and miRNA-144-5p in patients with depression, anxiety, or stress- and adjustment disorders after psychological treatment. *Cytokine* 146, 155646. <https://doi.org/10.1016/j.cyto.2021.155646>.
- Suzuki, H., Ohgidani, M., Kuwano, N., Chrétien, F., Lorin de la Grandmaison, G., Onaya, M., et al., 2019. Suicide and microglia: recent findings and future perspectives based on human studies. *Front. Cell Neurosci.* 13 <https://doi.org/10.3389/fncel.2019.00031>.
- Szabo, P.A., Dogra, P., Gray, J.I., Wells, S.B., Connors, T.J., Weisberg, S.P., et al., 2021. Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19. *e796 Immunity* 54 (4), 797–814. <https://doi.org/10.1016/j.immuni.2021.03.005>.
- Takahashi, T., Ellingson, M.K., Wong, P., Israelow, B., Lucas, C., Klein, J., et al., 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 588 (7837), 315–320. <https://doi.org/10.1038/s41586-020-2700-3>.
- Tan, J., Anderson, D.E., Rathore, A.P.S., O'Neill, A., Mantri, C.K., Saron, W.A.A., et al., 2021. Signatures of mast cell activation are associated with severe COVID-19. *medRxiv*. <https://doi.org/10.1101/2021.05.31.21255594>.
- Tendilla-Beltrán, H., Flores, G., 2021. Due to their anti-inflammatory, antioxidant and neurotrophic properties, second-generation antipsychotics are suitable in patients with schizophrenia and COVID-19. *Gen. Hosp. Psychiatry* 71, 137–139. <https://doi.org/10.1016/j.genhosppsych.2021.05.005>.
- Thakur, V., Jain, A., 2020. COVID 2019-suicides: a global psychological pandemic. *Brain Behav. Immun.* 88, 952–953. <https://doi.org/10.1016/j.bbi.2020.04.062>.
- Torres-Platas, S.G., Hercher, C., Davoli, M.A., Maussion, G., Labonté, B., Turecki, G., Mechawar, N., 2011. Astrocytic hypertrophy in anterior cingulate white matter of depressed suicides. *Neuropsychopharmacology* 36 (13), 2650–2658. <https://doi.org/10.1038/npp.2011.154>.
- Torres-Platas, S.G., Cruceanu, C., Chen, G.G., Turecki, G., Mechawar, N., 2014. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain Behav. Immun.* 42, 50–59. <https://doi.org/10.1016/j.bbi.2014.05.007>.
- Torres-Platas, S.G., Nagy, C., Wakid, M., Turecki, G., Mechawar, N., 2015. Glial fibrillary acidic protein is differentially expressed across cortical and subcortical regions in healthy brains and downregulated in the thalamus and caudate nucleus of depressed suicides. *Mol. Psychiatry* 21 (4), 509–515. <https://doi.org/10.1038/mp.2015.65>.
- Troyer, E.A., Kohn, J.N., Hong, S., 2020. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav. Immun.* 87, 34–39. <https://doi.org/10.1016/j.bbi.2020.04.027>.

- Turecki, G., Brent, D.A., 2016. Suicide and suicidal behaviour. *Lancet* 387 (10024), 1227–1239. [https://doi.org/10.1016/S0140-6736\(15\)00234-2](https://doi.org/10.1016/S0140-6736(15)00234-2).
- Turecki, G., Brent, D.A., Gunnell, D., O'Connor, R.C., Oquendo, M.A., Pirkis, J., Stanley, B.H., 2019. Suicide and suicide risk. *Nat. Rev. Dis. Prim.* 5 (1) <https://doi.org/10.1038/s41572-019-0121-0>.
- Vindegard, N., Benros, M.E., 2020. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav. Immun.* 89, 531–542. <https://doi.org/10.1016/j.bbi.2020.05.048>.
- Wang, Q., Roy, B., Turecki, G., Shelton, R.C., Dwivedi, Y., 2018. Role of complex epigenetic switching in tumor necrosis factor- α upregulation in the prefrontal cortex of suicide subjects. *Am. J. Psychiatr.* 175 (3), 262–274. <https://doi.org/10.1176/appi.ajp.2017.16070759>.
- Whitcroft, K.L., Hummel, T., 2020. Olfactory dysfunction in COVID-19. *JAMA* 323 (24), 2512. <https://doi.org/10.1001/jama.2020.8391>.
- World Health Organization, 2021. WHO Coronavirus (COVID-19) Dashboard. (<https://covid19.who.int/>) (Accessed September 2021).
- Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., et al., 2020. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm. Sin. B* 10 (5), 766–788. <https://doi.org/10.1016/j.apsb.2020.02.008>.
- Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., et al., 2020. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl. Acad. Sci. USA* 117 (20), 10970–10975. <https://doi.org/10.1073/pnas.2005615117>.
- Yang, A.C., Kern, F., Losada, P.M., Agam, M.R., Maat, C.A., Schmartz, G.P., et al., 2021. Dysregulation of brain and choroid plexus cell types in severe COVID-19. *Nature* 595 (7868), 565–571. <https://doi.org/10.1038/s41586-021-03710-0>.
- Zhao, Q., 2010. Dual targeting of CCR2 and CCR5: therapeutic potential for immunologic and cardiovascular diseases. *J. Leukoc. Biol.* 88 (1), 41–55. <https://doi.org/10.1189/jlb.1009671>.
- Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W., 2020. Single-Cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *Am. J. Respir. Crit. Care Med.* 202 (5), 756–759. <https://doi.org/10.1164/rccm.202001-0179LE>.
- Zhou, Y., Vedantham, P., Lu, K., Agudelo, J., Carrion Jr., R., Nunneley, J.W., 2015. Protease inhibitors targeting coronavirus and filovirus entry. *Antivir. Res* 116, 76–84. <https://doi.org/10.1016/j.antiviral.2015.01.011>.
- Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., et al., 2020. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl. Sci. Rev.* 7 (6), 998–1002. <https://doi.org/10.1093/nsr/nwaa041>.
- Zhou, Z., Ren, L., Zhang, L., Zhong, J., Xiao, Y., Jia, Z., et al., 2020. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. *Cell Host Microbe* 27 (6), 883–890. <https://doi.org/10.1016/j.chom.2020.04.017>.
- Ziegler, C.G.K., Allon, S.J., Nyquist, S.K., Mbano, I.M., Miao, V.N., Tzouanas, C.N., et al., 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 181 (5), 1016–1035. <https://doi.org/10.1016/j.cell.2020.04.035>.
- Ziegler-Heitbrock, L., Ancuta, P., Crowe, S., Dalod, M., Grau, V., Hart, D.N., 2010. Nomenclature of monocytes and dendritic cells in blood. *Blood* 116 (16), e74–e80. <https://doi.org/10.1182/blood-2010-02-258558>.
- Zortea, T.C., Brenna, C.T.A., Joyce, M., McClelland, H., Tippet, M., et al., 2020. The impact of infectious disease-related public health emergencies on suicide, suicidal behavior, and suicidal thoughts. *Crisis* 16, 1–14. <https://doi.org/10.1027/0227-5910/a000753>.