DIAGNOSTIC UTILITY OF INFLAMMASOMES AMONG SUBJECTS WITH BOH IN POST-COVID-19

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Abstract

The diagnostic utility of inflammasomes in Bad Obstetric History (BOH) following COVID-19 remains a critical area of investigation. COVID-19, which emerged in late 2019, and was caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has globally impacted health. The virus primarily targets Angiotensin-Converting Enzyme2 (ACE2) receptors, with elevated expression in various organs. Inflammasomes, integral to innate immunity, play a pivotal role in regulating proinflammatory responses, culminating in the release of cytokines and gasdermin-D-mediated pyroptosis. The pathophysiology of COVID-19 involves systemic inflammation, leading to a cytokine surge and instances of post-infectious Multi-system Inflammatory Syndrome (MIS). Diagnostic insights into inflammation post-COVID-19 rely on biomarkers such as IL-6, TNF-α and reactive oxygen species, with molecular probes facilitating imaging. A rigorous literature review was conducted using databases like PubMed, Google Scholar, Scopus, and Web of Science, focusing on studies (2015-2023) related to inflammasomes, proinflammatory cytokines, and serum markers in BOH post-COVID-19. Data from 76 selected articles were systematically extracted, categorized, and analyzed to identify diagnostic patterns and therapeutic interventions. The findings were synthesized into a manuscript emphasizing the diagnostic utility of inflammasomes, with multiple refinements ensuring clarity and scientific rigor. Exploring inflammasomes in BOH post-COVID-19 is promising, as inflammation and cytokine surges suggest their diagnostic potential. Further research is needed to confirm their role and improve diagnostic strategies for viral-induced inflammatory outcomes. This review explores the potential diagnostic significance of inflammasomes among subjects with BOH following COVID-19, emphasizing the need for a comprehensive understanding of the inflammatory processes associated with this unique clinical scenario.

Keywords: *Inflammasomes, Post-COVID-19, Multi-system Inflammatory Syndrome, Proinflammatory cytokines, Bad Obstetric History (BOH),* Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

1 Introduction

Covid-19, or coronavirus disease 2019, emerged in wuhan, china, in late december 2019. The world health organization (who) recognized its global threat and declared it a pandemic in march 2020. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (sars-cov-2), a single-stranded rna virus.[1,2] sars-cov-2 primarily targets angiotensin-converting enzyme 2 (ace2) receptors, which are abundantly present in lung epithelial cells, kidney proximal tubules, and tissues in the brain and heart.[3]

According to a 2017 study conducted by gomez-lopez and colleagues, inflammasomes are cytosolic multiprotein complexes that organize inflammation in reaction to pathogens and internal danger signals.[4] in 2014, de zoete et al., asserted that within the domain of innate immunity, inflammasomes, consisting of multiple proteins, play a pivotal role in regulating pro-inflammatory responses.[5] man et al., in 2017 highlighted the crucial involvement of inflammasomes in advancing the proteolytic cleavage process, leading to the release of proinflammatory cytokines (il-18, il-1β) and gasdermin-d. The n-terminal fragment of gasdermin-d is credited with initiating cytokine release and pyroptosis.[6]

Incidence and prevalence

In 2023, nune et al., identified 271 cases of rheumatic immune-mediated inflammatory diseases (r-imids) following covid-19 vaccinations in 39 countries from january 2021 to may 2023. The mean age was 56, with 62.5% being females, and prevalent conditions included vasculitis (31.7%) and connective tissue disease (24.3%), typically emerging within 11 days post-vaccination. The study underscores a potential association between sars-cov-2 vaccines and r-imids, emphasizing the necessity for further epidemiological investigations.[12]

2 Methodology

1. **Literature search:** a rigorous literature review was conducted to identify articles on the diagnostic utility of inflammasomes in boh following covid-19. Systematic searches were performed on major electronic databases, including pubmed, google scholar, scopus, and web of science. Keywords such as "inflammasomes," "post-covid-19," "multisystem inflammatory syndrome," "proinflammatory cytokines" "bad obstetric history," "therapeutic intervention," "inflammatory conditions," and "serum markers" were employed. The search spanned studies published between 2015 and 2023, aligning with the knowledge cutoff date in january 2022.
2. **Review method and selection criteria:** the review method and selection criteria were delineated to ensure a focused approach. Inclusion criteria encompassed studies exploring the diagnostic role of inflammasomes in boh subsequent to covid-19, with a specific focus on proinflammatory cytokines, therapeutic interventions, and serum markers. Both experimental and observational studies, as well as reviews, were considered. Exclusion criteria comprised studies not in english, case reports, and those lacking methodological rigor.

3. **Data extraction:** a systematic approach was employed for data extraction, capturing essential details from selected articles, including study design, diagnostic parameters, methodologies, and key findings. A standardized extraction form was used to maintain consistency and accuracy.

4. **Data synthesis:** the extracted data were categorized and analyzed to discern patterns, differences, and trends related to the diagnostic utility of inflammasomes in boh after covid-19. This comprehensive synthesis aimed to unravel the role of proinflammatory cytokines, therapeutic interventions, and serum markers in the context of inflammatory conditions.

5. Manuscript writing: the manuscript, built upon synthesized data from the selected 76 articles spanning 2015-2023, focused on the diagnostic utility of inflammasomes in boh following covid-19. Emphasis was placed on proinflammatory cytokines, therapeutic interventions, and serum markers. The writing process involved multiple refinements to ensure clarity, coherence, and adherence to scientific writing standards.

Inflammasome activation and ligand response in the context of post-covid-19 syndrome

De rivero vaccari and colleagues in 2016 emphasized that inflammasomes respond differently to various ligands, which can be categorized as either endogenous or exogenous. They identified sars-cov-2 as a pathogen-associated molecular pattern (pamp) capable of activating inflammasomes. This insight is crucial for understanding the potential diagnostic significance of inflammasomes in post-covid-19 syndrome.[13]

Two-step mechanism of inflammasome activation

Examining the work of kigerl and co-authors in 2014, the two-step mechanism involved in inflammasome activation is elucidated. Signal 1, or the priming step, involves the binding of pamps or damps to pattern recognition receptors (prrs), such as toll-like receptor (tlr)-4, triggering the synthesis of pro-il-1β and pro-il-18 in a nuclear factor (nf)-κb-dependent manner. This understanding is foundational for exploring the diagnostic potential of inflammasomes in the post-covid-19 setting.[14]

Mechanisms driving inflammasome formation

Delving into the insights of de vasconcelos and lamkanfi in 2020, the secondary signal required for inflammasome formation and the conversion of pro-il-1β and pro- il-18 into their active forms are detailed. Mechanisms, including the gsdm-d pore formation, shed light on the intricate processes that may have diagnostic implications in the post-covid-19 period.[15]

Assembly and activation cascade of inflammasomes

Under the investigation of de rivero vaccari and colleagues in 2009, the assembly and activation cascade of inflammasomes are explored. The oligomerization of sensor molecules, recruitment of the adaptor protein asc, and the integration of caspase-1 are critical steps. Understanding these processes becomes integral in evaluating the diagnostic utility of inflammasomes in the context of individuals experiencing lingering symptoms, such as those with post-covid-19 syndrome.[16]

Diagnostic insights into inflammation and inflammasomes in post-covid-19 conditions

The key pathophysiology of covid-19 infection, particularly in moderate and severe cases, involves systemic inflammation, driven by various pro-inflammatory cytokines contributing to the cytokine surge.[17] while the inf lammatory state usually diminishes during the recovery phase, instances of a post-infectious hyperinflammatory stage termed multisystem inflammatory syndrome (mis) have been reported.[18,19] based on the studies conducted by sugimoto et al. In 2019 and sun et al. In 2020, the identification of inflammation through imaging hinges on fundamental biomarkers. These markers encompass a range of inflammatory factors like interleukin-6 (il-6), tumor necrosis factor-α (tnf-α), and reactive oxygen species (ros), including hydrogen peroxide (h2o2), hypochlorous acid (hclo), and peroxynitrite (onoo–).[20,21] diverse molecular probes have been developed for both in vitro and in vivo imaging of inflammation, as reported by yangb et al., in 2023 and lin et al., in 2022.[23,24]

Preterm birth, identified as a widespread and detrimental obstetrical syndrome by romero et al., in 1994 and gotsch et al., in 2009, stands as the leading cause of perinatal morbidity and mortality worldwide, as emphasized by blencowe and colleagues in 2012.[24,25,26] theoretically, physiological and immunological changes in pregnancy, as observed in encounters with other coronaviruses (chen et al., 2020), may increase the susceptibility of pregnant women to both general and severe morbidity associated with covid-19.[27]

Activation of inflammasome

The inflammasome is a multiprotein complex that plays a key role in activating caspase-1, which in turn leads to the activation of interleukin-1 beta (il-1β). This process occurs in various diseases and infections, including those caused by coronaviruses, and is observed in tissues such as the lungs, brain, intestines, and kidneys, all of which have shown alterations in covid-19 patients.[28]

In 2016 broz et al., highlighted that inflammasomes are cytosolic protein complexes that form in response to various stimuli. These large, micrometer-scale cytosolic complexes assemble in response to pathogen-associated molecular patterns (pamps) or damage-associated molecular patterns (damps), triggering the release of proinflammatory cytokines and inducing pyroptosis, a form of proinflammatory lytic cell death. [29,30] importantly, inflammasomes are not only crucial for defending against infections but also play a significant role in the development of various human inflammatory disorders.[30]

Active interleukin-1β (il-1β) and interlukin-18 (il-18) stand out as key indicators of the inflammatory response facilitated by inflammasomes among the proinflammatory cytokines.[31] recent findings indicate a crucial involvement of inflammasomes in the progression of covid-19 towards severe outcomes. Initially, it was demonstrated that the inflammatory cytokine il-6 is linked to the severity of covid-19.[32] significantly, heightened plasma concentrations of il-6 correlate with increased serum levels of lactate dehydrogenase, a cytosolic protein released from dying cells in inflammatory processes.[33] an advanced longitudinal study on covid-

19 patients identified a connection between late-stage covid-19 pathology and cytokines linked to the inflammasome pathway, specifically il-1β and il-18 [34]. Consistent with these observations, our research, along with that of others, has shown that sars-cov-2 infection induces inflammasome activation. The extent of this activation in covid-19 patients correlates with disease severity, suggesting that sars-cov-2-driven inflammasome activation exacerbates the clinical outcomes in these patients. [35,36,37]

Biomarkers

The progression of post-covid syndrome (pcs) is linked to the severity biomarkers observed in covid-19 cases. For example, individuals who have survived covid-19 and exhibit elevated d-dimer and blood urea nitrogen levels three months post-hospital discharge are at a higher risk of developing pulmonary dysfunction, contributing to pcs. [38,39] similarly, heightened levels of crp, d-dimer, and il-6 are associated with both pulmonary issues and the progression of pcs .[40] additionally, raman et al., in 2021 found a connection between increased systemic inflammation biomarkers, lymphopenia, and radiological lesions in various organs within three months of covid-19 survivors being discharged.[41] notably, elevated troponin levels are linked to fatigue development, and lymphopenia is correlated with an increased likelihood of tachycardia in pcs patients. Therefore, examining persistent symptoms in covid-19 survivors requires consideration of inflammatory biomarkers and lymphocyte counts to predict pcs development .[42]

In 2020 ponti g and co-authors, suggested that, there is a critical need for new biomarkers that can accurately pinpoint individuals at risk of experiencing rapid disease progression leading to severe complications and mortality. The discovery of such biomarkers is intricately linked to comprehending the pathogenesis of the viral infection, as well as the associated cellular and organ damage. The development of effective biomarkers holds significant potential for enhancing screening processes, refining clinical management strategies, and preventing the onset of severe complications.[43]

Creatinine, albumin, interleukin-6, ferritin, c-reactive protein (crp), hs troponin i, total bilirubin, blood urea nitrogen (bun), nt-probnp, procalcitonin (pct), and blood gas levels are part of the immune-inflammatory and coagulation pathways.[44] these laboratory biochemical parameters are taken into consideration. Thus, these laboratory biomarkers are crucial to the patient admission process, the evaluation of the disease's staging based on severity and prognosis, patient monitoring, and treatment recommendations.[44,45,46] additional nonspecific biomarkers indicating cellular damage and inflammation comprise lactate dehydrogenase (ldh) and aspartate aminotransferases (ast, alt) .[47,48]

In addition to traditional and non-specific biomarkers, organ-specific biomarkers, including cardiac, liver, and kidney markers, are recognized. Beyond these, novel biomarkers have been identified, namely mid-regional pro-adrenomedullin (mr-pro-adm), monocyte distribution width (mdw), and mirnas.[49] emerging technologies for biomarker measurement encompass both conventional and unconventional methods. Traditional approaches of biomarker measurement

involve salivary biomarker measurement and digital immunoassays, while non-conventional methods include biosensors based on chips, paper, thread, and film.[50] electrochemical, optical, and microfluidic biosensors show promise in measuring levels of biomarkers such as crp, pct, il-6, and ferritin. These methods offer advantages such as high sensitivity, reliability, and relatively low cost.[51]

Imaging techniques for assesing the activation of inflammasomes

Plasma, pbmc, and neutrophils isolation

Ten milliliters of peripheral blood were obtained from patients through indwelling venous catheters and from healthy controls through venipuncture using edta tubes. Plasma separation was achieved by centrifuging seven milliliters of blood for 10 minutes at 450 × g. For the isolation of peripheral blood mononuclear cells (pbmcs) and neutrophils, three milliliters of whole blood were layered onto two distinct density histopaque gradients and centrifuged for 30 minutes at 872 × g. Pbmcs were collected from the first layer, while neutrophils were isolated from the second buffy coat layer. The cells were then washed twice with rpmi without phenol red at 200 × g for 10 minutes and quantified.

Neutrophils obtained from either covid-19 patients or healthy controls were incubated with rpmi 1640 supplemented with 10 mm n-2-hydroxyethylpiperazine-n9-2-ethanesulfonic acid. Subsequently, neutrophils and pbmcs were affixed to slides for 30 minutes at 37°c before fixation with 4% paraformaldehyde (pfa) for 30 minutes at room temperature (rt) prior to staining. Additionally, healthy human neutrophils attached to the slides were stimulated, as indicated, at 37°c, 5% co2 with 5 mg/ml lipopolysaccharide (lps) before fixation with 4% pfa for 30 minutes at rt .[52]

Il-1b measurement in supernatant

Neutrophils isolated from healthy individuals were seeded at a density of 5 × 10^6 cells per ml in 48-well plates. These cells were then stimulated with 5 mg/ml lipopolysaccharide derived from *klebsiella pneumoniae* for a duration of 4 hours at 37°c under 5% co2. Subsequently, culture supernatants were collected, and non-adherent cells were eliminated through centrifugation. The concentration of supernatants was adjusted using 0.5 centrifugal filter units (millipore) following the manufacturer's protocol. The quantification of il-1b in the supernatants was performed using an enzyme-linked immunosorbent assay in accordance with the manufacturer's instructions.[52]

Tracheal aspirates

To obtain tracheal aspirate from covid-19 patients, the endotracheal tube was aspirated. The acquired fluids were combined in a 1:1 ratio with 0.1 m dithiothreitol, followed by a 10-minute incubation at room temperature. The mixture was then centrifuged at 400 × g at rt for 10 minutes. Tracheal smears were conducted on glass slides and subsequently fixed with 4% paraformaldehyde for 1 hour before proceeding to immunostaining.[52]

Immunofluorescence

Fixed cells were subjected to a single wash with phosphate-buffered saline (pbs), permeabilized for 10 minutes at 4°c, and then treated with blocking buffer (2.5% bovine serum albumin, 0.5% tween-20 in 1/3 pbs) at 37°c for 1 hour.

Subsequently, the samples were incubated overnight at 4°c with the following primary antibodies: rabbit anti-citrullinated histone h3 (1:500), rabbit anti-asc (1:400), and mouse anti-cd66b (1:500). Following pbs washes, the samples were exposed to secondary antibodies: donkey anti-mouse immunoglobulin g (1:1500) or donkey anti-rabbit (1:1500). After three additional washes with pbs, the samples were mounted using a medium containing 4',6-diamidin-2-phenylindole (dapi). Visualization of images was carried out on an fluorescence microscope equipped with an monochromatic ccd camera and a oil differential interference contrast (dic) objective lens, utilizing the software. Images were uniformly acquired and processed with software. For confocal microscopy, immunostainings were imaged on a confocal microscope using a 100x oil objective.[52]

Flow cytometry

The assembly of the inflammasome complex was assessed by detecting asc speck formation using imaging flow cytometry. In brief, peripheral blood mononuclear cells (pbmcs) were treated with the fluorochrome inhibitor of caspase-1/4/5 following the manufacturer's instructions. This involved a 50-minute incubation at 37°c to allow flica binding to activated inflammatory caspases. After two washes with the flica kit wash buffer, cells were incubated with live/dead fixable aqua dead cells stain for 15 minutes at room temperature. Extracellular staining was performed in pbs + 1% bsa using fluorochrome-conjugated antibodies for monocyte phenotyping, including anti-cd14 bv605 (clone: m5e2), anti-cd16 pe-cy7 (clone: 3g8), and anti-cd3 pe (clone: hit3a).

After fixation and permeabilization with cytofix/cytoperm overnight at 4°c, cells were stained for 1 hour at room temperature for intracellular asc using anti-asc/tms1 af647 antibody. Simultaneously, cells were stained with monocyte markers and 200 nm mitotracker red , followed by asc intracellular staining for the evaluation of mitochondrial membrane potential. Cell acquisition was performed using a 12-channel amnis imagestreamx mark ii imaging flow cytometer, and data collection utilized the integrated software inspire. Image analysis was conducted using image-based algorithms in the image stream data exploration and analysis software.[53]

Clinical presentation of inflammasome-associated symptoms

Inflammasomes, which are multimeric complexes, are formed in response to various physiological and pathogenic triggers. These complexes play a crucial role in the innate immune response, significantly contributing to the elimination of pathogens or damaged cells.[54] the innate immune system acts as the first line of defense against invading pathogens, relying on pattern-recognition receptors (prrs) encoded in the germline. These receptors are found on the cell surface, within endosomes, and in the cytoplasm. Toll-like receptors (tlrs) are located on membranes, while nod-like receptors (nlrs), aim2-like receptors (alrs), and rig-i-like receptors are situated in the cytoplasm.

Of particular importance, nlrs and alrs have the ability to assemble into inflammasomes, which are crucial for initiating inflammatory responses. The dysregulation of these multi-protein complexes has been implicated in various inflammatory disorders, each characterized by a distinct clinical profile.

Understanding the intricate mechanisms of inflammasome activation and their role in the immune response provides valuable insights into the pathogenesis of inflammatory diseases and may pave the way for targeted therapeutic interventions.[55]

Characteristic features in post-covid-19 multisystem inflammatory syndrome

The association between covid-19 and a multisystem inflammatory syndrome in children and adolescents (mis-c) has been well established, while limited reports in adults describe a comparable phenomenon. In 2020 , ahsan and rani along with jiang et al. And sadiq et al. 2020 , have highlighted the well-documented occurrences of mis-c and kawasaki-like disease in children following sars-cov-2 infection.[56,57,58] however, the manifestation of a similar syndrome in adults is infrequently reported. Ellul et al., in 2020 expanded on this, noting that neurological involvement, including guillain-barré syndrome, has been observed in a small number of patients post-covid-19 infection.[59] this underscores the diversity of clinical manifestations associated with covid-19 across different age groups and emphasizes the need for continued research to comprehensively understand the spectrum of post-infection sequelae in both children and adults.

Morris et al., in 2020 noted that severe sars-cov-2 infection typically involves hyperinflammation and respiratory failure, whereas mis-a, a recently recognized condition, shows minimal respiratory symptoms. The persistence of the virus in various organs, along with endothelial inflammation and thrombo-inflammatory processes, is suggested as potential mechanisms for post-covid mis-a. Laboratory abnormalities extend beyond inflammatory markers, encompassing liver function and coagulation parameters. Diagnosis involves excluding other potential causes and confirming a history of covid-19. [60]

Therapeutic implications

Li and co-authors in 2021 underscored the importance of gaining a more profound understanding of the signaling molecules orchestrating the activation of inflammasomes.[61] this deeper comprehension is deemed crucial for harnessing the therapeutic potential of inflammasomes. In alignment with this perspective, pirzada et al., in 2020 reiterated the significance, emphasizing the promise of therapeutic interventions directed at the inflammasome complex for the treatment of associated diseases. Notably, recent strides in research have embraced innovative approaches, such as machine learning and artificial intelligence, contributing to the acceleration of drug development in this field.[62]

The potential of inflammasome modulation as a strategy for treating chronic inflammatory diseases gains further support from insights provided by ozaki and collaborators in 2015.[63] their contribution highlights the centrality of identifying small-molecule inhibitors in the intricate landscape of inflammasome research. Recognizing these inhibitors is positioned as a pivotal step, crucial for advancing the development of effective therapeutic strategies tailored to address the complexities of chronic inflammatory conditions.

Al-hilli and al-mosawi in 2016 defined bad obstetric history (boh) as indicative of previous adverse fetal outcomes, encompassing two or more consecutive spontaneous abortions, early neonatal deaths, stillbirths, intrauterine fetal deaths, intrauterine growth retardation, and congenital anomalies.[64] dimitriadis et al., in 2020 expanded on this by asserting that the prognosis for couples experiencing recurrent pregnancy loss is generally favorable, though the likelihood of a successful pregnancy is influenced by maternal age and the number of previous losses. Recurrent pregnancy loss can be attributed to factors such as chromosomal errors, anatomical uterine defects, autoimmune disorders, and endometrial dysfunction.[65]

Furthermore, in 2015 shawe et al., underscored the significance of preconception care in the context of boh. They emphasized its importance in screening, preventing, and managing risk factors that can impact pregnancy outcomes. Preconception care becomes a crucial component in optimizing the chances of a successful and healthy pregnancy. The collective insights from these studies highlight the multifaceted nature of boh, urging a comprehensive approach that includes both understanding the causative factors and implementing proactive measures to enhance pregnancy outcomes.[66] according to cirino and co-authors in 2017, genetic testing not only influences how results are interpreted compared to traditional laboratory diagnostics but also affects their application. The study highlights the presence of significant depression and anxiety in women during the first month following early pregnancy loss, with partners also exhibiting lower but notable levels of depression and anxiety. Beyond medical interventions, continuous support is deemed crucial during this challenging period.[67]

Additionally, in 2020, dimitriadis et al., emphasized that recurrent pregnancy loss may result from various factors such as chromosomal errors, anatomical uterine defects, autoimmune disorders, and endometrial dysfunction. While available treatments target these putative risk factors, the effectiveness of many medical interventions remains a subject of controversy. Collaborative care with a healthcare provider, especially one specializing in reproductive or maternal-fetal medicine, is stressed as essential. Such personalized approaches aim to optimize the chances of achieving a successful and healthy pregnancy.[65] the comprehensive insights from these studies underscore the multifaceted nature of reproductive health, calling for a combination of genetic understanding, emotional support, and tailored medical interventions.

Case studies

In a study led by jiang et al., in 2020, findings reveal the ongoing global spread of severe acute respiratory syndrome coronavirus 2 (sars-cov-2). Notably, there is a rising number of documented cases among children and adolescents in europe, north america, asia, and latin america, characterized by multisystem inflammatory conditions associated with covid-19. Despite constituting a relatively small percentage of total covid-19 cases, children and adolescents are increasingly being recognized as affected populations.[69]

The research underscores that national statistics from various countries in asia, europe, and north america indicate that pediatric cases represent a range of 2.1% to 7.8% of confirmed covid-19 cases. The recognition of such patterns in different regions highlights the importance of monitoring and understanding the impact of covid-19 on diverse demographic groups, particularly among the younger population.[68,69,70,71]

According to the research conducted by yasuhara and co-authors in 2021, it is suggested that multisystem inflammatory syndrome in children (mis-c) can lead to multiple organ failure, encompassing manifestations in the gastrointestinal system, myocardial dysfunction and coronary abnormalities. The distinct characteristics of mis-c set it apart from kawasaki disease, as noted by the researchers. Expanding on the definition within the united kingdom, mis-c is described as a spectrum of illness ranging from persistent fever and inflammation to displaying characteristic features akin to kawasaki disease in children.[72] furthermore, the spectrum extends to encompass severely ill children experiencing shock and multiple organ failure. This comprehensive definition has been proposed by the royal college of paediatrics and child health, as outlined by levin m in 2020.[73,74]

In the investigations conducted by menikou et al., in 2021 and levin et al., in 1985, it was discovered that the virus may serve as an immune trigger, leading to immune-mediated injury in the heart and coronary arteries. This injury is comparable to the pathological mechanisms observed in kawasaki disease.[75,76] these findings underscore the potential role of the virus in instigating immune responses that result in cardiac and vascular complications, contributing to our understanding of the complex manifestations associated with mis-c.

3 Conclusion

The diagnostic exploration of inflammasomes in boh following covid-19 is a promising avenue. The systemic inflammation and cytokine surge observed in covid-19, coupled with the potential for a post-infectious hyperinflammatory state, underscore the importance of unraveling the role of inflammasomes. Insights from this review suggest that molecular probes and biomarkers used for inflammation detection post-covid-19 may offer valuable clues in understanding boh. However, further research is imperative to establish the link between inflammasomes and boh conclusively. This investigation holds potential implications for refining diagnostic strategies and contributing to a deeper comprehension of the intricate interplay between viral infections, inflammation, and neurological manifestations.

Conflict of interest

There are no conflicts of interest related to this study.

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Author’s contribution

ТАБЛИЦЫ

Table 1. Table indicating inflammasomes involved in COVID-19 and Bad Obstetric History (BOH)

Inflammasomes	Associated Clinical Conditions	Mechanism of Action	Reference
NLRP3 Inflammasome	COVID-19 and BOH	The mechanism involves recognizing viral RNA, initiating an inflammatory cascade, and contributing to the severe cytokine storm observed in severe cases.	[7,8]
AIM2 Inflammasome	COVID-19	In COVID-19, AIM2 inflammasome recognizes viral DNA, activating and releasing pro-inflammatory cytokines, contributing to the host's immune response; however, dysregulation may lead to the cytokine storm seen in severe cases.	[9]
NLRC4 Inflammasome	COVID-19	In COVID-19, NLRC4 inflammasome activates in response to bacterial co-infections, releasing pro-inflammatory cytokines and influencing the overall severity of the immune response.	[10]
NLRP1 Inflammasome	Autoimmune diseases and inflammatory conditions	In autoimmune diseases and inflammatory conditions, NLRP1 inflammasome activates, triggering release of pro-inflammatory cytokines and modulating immune responses.	[11]

РИСУНКИ

Figure 1. Methods of literature search

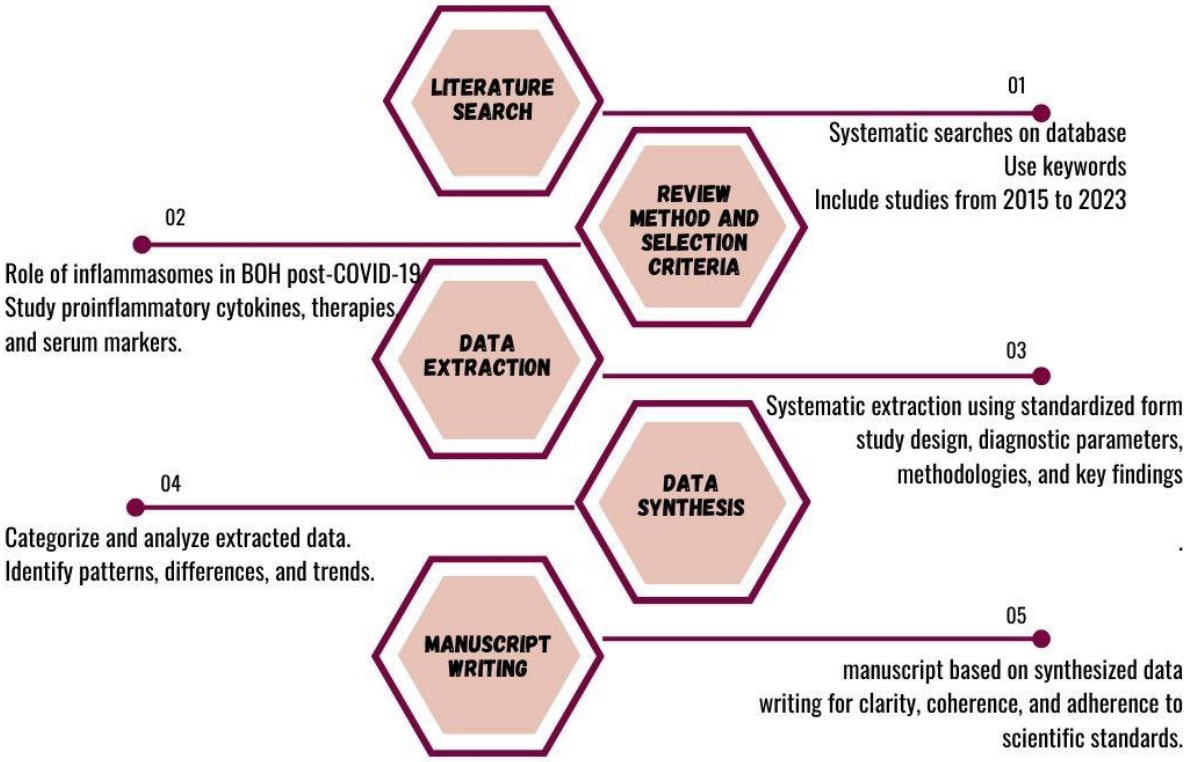
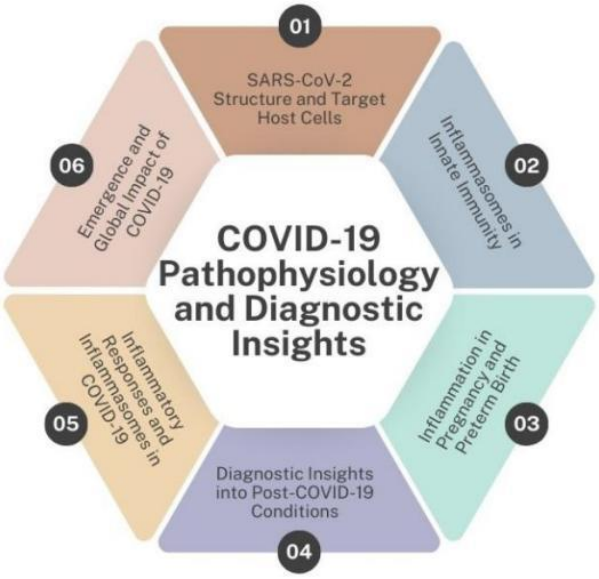


Figure 2. Overview of covid-19 pathophysiology and diagnostic insights



ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи
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Сокращенное название статьи для верхнего колонтитула:

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Reference sequence number	Authors, title of a publication and source where it was published, publisher's imprint	Full name, title of a publication and source in English	Reference's URL and/or doi
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