

RATIONALE FOR POLYCLONAL INTRAVENOUS IMMUNOGLOBULIN ADJUNCTIVE THERAPY IN COVID19 PATIENTS: REPORT OF A STRUCTURED MULTIDISCIPLINARY CONSENSUS

Running Title: Immunoglobulin Therapy and COVID19

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ABSTRACT

INTRODUCTION

Adjunctive therapy with polyclonal intravenous immunoglobins (IVIg) is currently used for preventing or managing infections and sepsis, especially in immunocompromised patients. The pathobiology of COVID19 and the mechanisms of action of Ig led to consider this adjunctive therapy also in patients with respiratory failure by SARS-CoV2 infection. This manuscript report the rationale, the available data and the results of a structured consensus on intravenous Ig therapy in patients with severe COVID19.

METHODS

A panel of multidisciplinary experts defined the clinical phenotypes of COVID19 patients with severe respiratory failure and, after literature review, voted for the agreement on the rationale and the potential role of IVIg therapy for each phenotype. Due to the scarce evidence available, a modified RAND/UCLA appropriateness method was used.

RESULTS

Three different phenotypes of COVID19 patients with severe respiratory failure were identified: patients with an abrupt and dysregulated hyperinflammatory response (early phase), patients with suspected immune-paralysis (late phase), and patients with sepsis by hospital-acquired superinfection (sepsis by bacterial superinfection). The rationale for intravenous Ig therapy in the early phase was considered uncertain whereas the panellists considered appropriate its use in the late phase and patients with sepsis/septic shock by bacterial superinfection.

CONCLUSION

As with other immunotherapies, IVIg adjunctive therapy may a potential role in the managing of COVID19 patients. The ongoing trials will clarify the appropriate target population and the true effectiveness.

Key Words: Respiratory Failure, COVID19, Intravenous Immunoglobulin Therapy

INTRODUCTION

Since February 20th, 2020 Italy has been overwhelmed by the SARS-CoV-2 virus outbreak and several patients with interstitial pneumonia and respiratory failure requiring mechanical ventilation were admitted to intensive care units (ICUs), threatening the capability of health care systems to handle this amount of critical patients [1]. Unfortunately, so far there are few validated therapies to prevent or treat the severe acute respiratory distress syndrome (ARDS) caused by this novel virus and, thus, the case-fatality rate in patients admitted to ICU is extremely high [2–7]. Therefore, along with the maintenance of vital functions by supportive treatments, effective therapies in COVID19 are urgently needed.

In the last months, the scientific community provided a tremendous improvement in the knowledge of mechanisms involved in COVID-19 pathobiology. The first model used to describe severe patients with COVID-19 included an uncontrolled immune response characterized by systemic hyper inflammation with an abnormal increase of circulating cytokines and chemokines (the so-called cytokine storm) with a pivotal role in lung tissue damage, increase in vascular permeability and clots formation, akin to secondary hemophagocytic lymphohistiocytosis (sHLH) and macrophage activation syndrome (MAS) [8–11]. The COVID-19-associated cytokine storm is associated with elevated plasma levels of IL-6, IL-1, and TNF- α , as well as ferritin and other inflammatory biomarkers. However, a recent study, reporting cytokine levels in different subsets of critically ill patients, showed that in COVID-19 patients with ARDS the circulating levels of these cytokines were lower compared to those measured in patients with bacterial sepsis, and similar to those with other causes of ARDS, trauma and out-of-hospital cardiac arrest [13]. Despite the limitations of the study, this may suggest that COVID-19 severe illness may be more than a cytokine storm, acting with more complex mechanisms involving innate and cellular immune response [14]. Different studies have explored the derangements of the immune system during COVID-19 and the associations with the outcome [15,16]. First, a key feature of severe patients with COVID-19 is represented by progressive lymphopenia with marked CD-4 and CD-8 T cell exhaustion [17–19]. More recently, COVID-19 clinical syndrome and related immunopathogenesis have been compared with sepsis, recalling the need to target the underlying and shared impairment of protective T cell immunity, while suppressing the emergent cytokine storm [20–22]. Indeed, Hotchkiss et al described the similarities between the course of immune activation and suppression during sepsis and COVID-19, suggesting that in the former—the hyperinflammatory peak may be higher ~~than~~—and the immunosuppressive phase may be deeper and earlier in the latter. This trend may be also reinforced by the use of immunosuppressive agents (e.g. steroids and cytokine blocking agents) introduced in the treatment of patients with COVID-19 and respiratory failure [23]. Further investigations are warranted to clarify the relationships between these clinic and immunologic features in severe COVID-19 patients, possibly indicating the need to modulate the host immune response with immunotherapeutic treatments.

IMMUNOGLOBULIN ADJUNCTIVE THERAPY

As described above, sepsis and septic shock result from a complex dysregulation of the inflammatory and immune response [24] that is quite similar to immunological derangement observed in COVID-19 critical patients. Immunoglobulins have pleiotropic effects on the inflammatory-immune response including toxin scavenging, microbial phagocytosis, anti-inflammatory effects and anti-apoptotic actions on immune cells [21,27,28,31,33]. Although guidelines do not indicate the use of intravenous polyclonal immunoglobulin (IVIg) in patients with bacterial infections [29], several studies showed a potential benefit in patients with sepsis and septic shock [27,30–33] and IVIg are commonly used as adjunctive therapy in immune-compromised patients with infections [34,35]. Therefore, adjunctive therapy with IVIg may have also a rationale

in the management of COVID19 patients that depends on the disease phase and the related pathobiological phenotype. For instance, despite the role of persistent viremia and viral activity in tissues is unclear, Ig may have a role in the early phases of COVID19 by reducing the viral burden and by scavenging or down-regulating the production of the high levels of inflammatory mediators. In the late phases, especially in ICU patients with secondary bacterial infections, IVIg may have an important synergic activity in the empowerment of antibiotic efficacy and in supporting the overt immune-dysfunction [36]. (Figure 1)

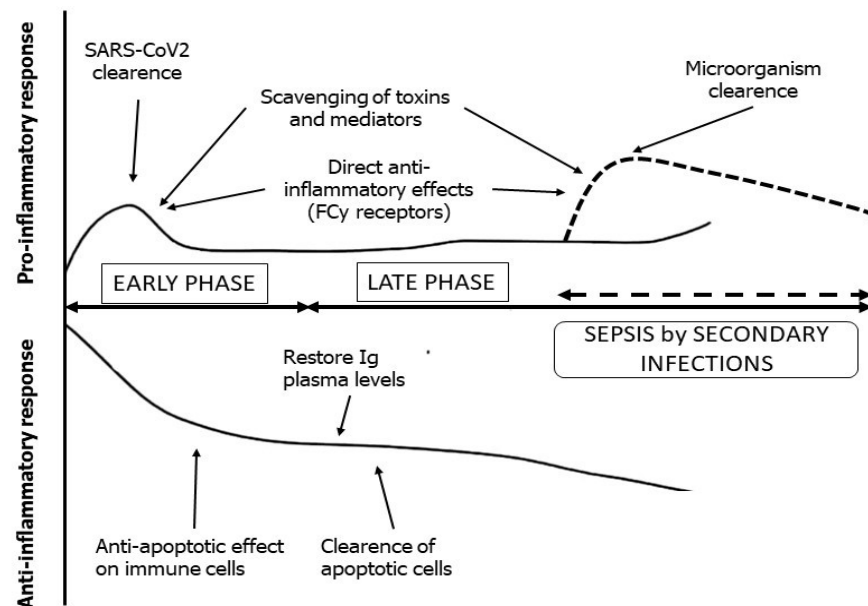


Figure 1: Host immune-inflammatory response in COVID19 (modified from Remy et al. Lancet Respir Med. 2020 Oct;8(10):946-949). The potential role of immunoglobulins in pro and anti-inflammatory response and the three scenarios (i.e. early, late, sepsis by secondary infections) identified by the panel are also reported

Currently, clinical data supporting the use of adjunctive therapy with IVIg in the management of COVID-19 are limited [37–42]. A recent multicentre retrospective cohort study evaluated the efficacy of adjunctive therapy with IVIg by comparing 172 critically ill COVID19 patients who received IVIg at a dose of 0.1– 0.5 g/kg/day for 5–15 days to 151 patients critically ill COVID19 patients who did not receive IVIg [37]. They observed that early administration (≤ 7 days postadmission) of high-dose IVIg improves the prognosis of critical-type patients with COVID-19 with a 20% absolute risk reduction in 28-day mortality. Another retrospective study also confirmed the therapeutic benefits of IVIG when therapy was initiated early [41]. A small pilot randomised controlled study (16 vs 17 patients) showed that IVIg 0.5g/kg daily for 3 days with concomitant methylprednisolone reduce the progression of respiratory failure requiring mechanical ventilation and improved oxygenation at 7 days in COVID-19 patients with $\text{Pao}_2 / \text{Fio}_2 < 140$ [40]. Several phase 2 and 3 trials are underway to confirm the above preliminary observations (ClinicalTrials.gov Identifier: NCT04432324, NCT04500067, NCT04576728, NCT04350580, NCT04350580).

This manuscript reports the results of a structured process of consensus among experts aimed to discuss the rationale for adjunctive therapy with IVIg and to identify the phenotype of

COVID19 patients who could benefit the most based on the pathobiology of COVID19 and pharmacological effects of IVIg adjunctive therapy.

CONSENSUS METHODOLOGY

The moderator (MG) selected nine experts in the field of intensive care medicine and infectious diseases to create a multidisciplinary panel. All panellists had a high research profile with large clinical experience in the management of COVID-19 patients and IVIg adjunctive therapy and were well experienced in procedures of structured consensus.

In the first meeting, after an initial discussion on the main difficulties in COVID-19 management, the panellists defined the methods for the consensus, and the different phenotypes of COVID-19 patients with severe respiratory failure based on the time course of the disease, the clinical presentations and the underlying pathophysiological features. Three different clinical scenarios were identified: i) EARLY PHASE: patient with an abrupt and dysregulated hyperinflammatory response; ii) LATE PHASE: patient with suspected immune-dysfunction or immune-paralysis; and iii) SEPSIS BY BACTERIAL SUPERINFECTION: patient with sepsis or septic shock by hospital-acquired superinfection. For this consensus, SARS-CoV-2 infection was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs or lower respiratory tract specimens. Moderate to severe ARDS was defined as new or worsening respiratory failure with bilateral opacities and $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg with positive end-expiratory pressure ≥ 5 cmH₂O not fully explained by cardiac failure, fluid overload, pleural effusions and lobar or lung collapse [43].

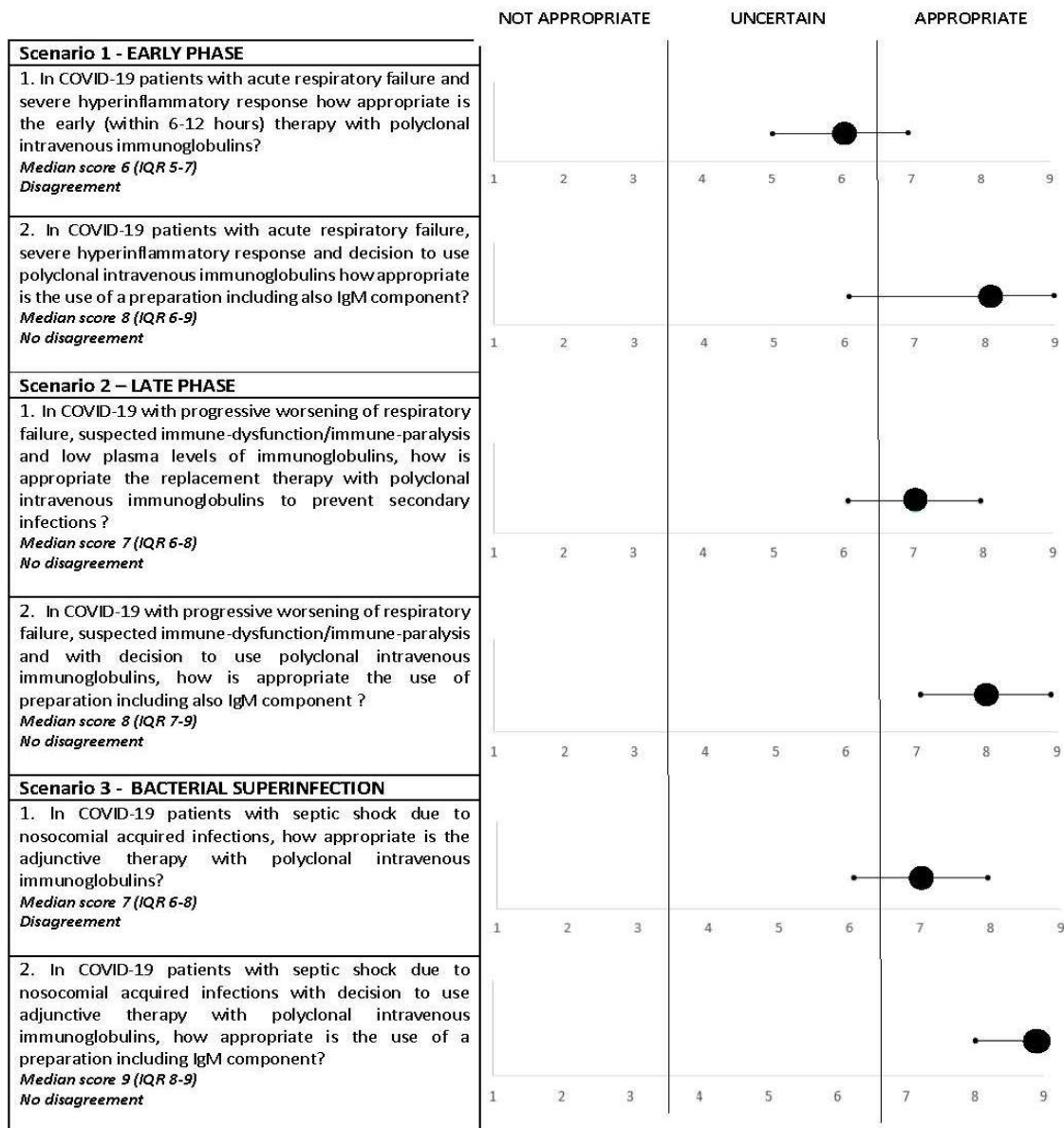
The treatment selected was polyclonal intravenous immunoglobulin (IVIg) administration, including polyclonal IgG preparations that contain at least 96% of polyclonal IgG and IgM-enriched preparations which composition is polyclonal IgG 76%, IgM 12% and IgA 12%. IVIgM preparations, compared to IVIg, seem to provide a better clinical effect in septic patients [44,45] due to the IgM component and its fundamental role in innate immune response [46].

Due to the scarce evidence available on immunoglobulin treatment for COVID-19 patients with respiratory failure, the panellists decided to use a modified semiquantitative RAND/UCLA appropriateness method [47]. This semiquantitative allows each component of the panel to express an opinion not influenced by other experts and allows also to supply to the lack of evidence with the experience and opinion of the panellists.

A systematic review of literature according to population, treatment and relevant outcome was performed using three electronic databases: PubMed, EMBASE and Scopus. All the literature material was readily available at any time for all the panellists. The coordinator of the panel (MG) analysed the literature that was presented to the other panellists during a second structured meeting. During this meeting, the list of clinical scenarios and treatments were better redefined to avoid uncertainties in the rating procedures. An online voting system was used for the final anonymous vote. The panellists had to rate each clinical scenario as 'appropriate', 'inappropriate' or 'uncertain' on a scale of 1 to 9 points, with 1=completely inappropriate and 9=fully appropriate. The median of the ratings of all panellists was calculated, and we defined as inappropriate a scenario with a median value from 1 to 3, uncertain from 4 to 6 and appropriate from 7 to 9. 'Disagreement' for each scenario was defined when more than 3 panellists rated outside the 3-point region (1-3, 4-6 and 7-9) containing the median [47].

CONSENSUS RESULTS

(see Figure 2)

SCENARIO 1, EARLY PHASE: COVID-19 interstitial pneumonia with an abrupt and dysregulated hyperinflammatory response.**Figure 2:** Results of the appropriateness evaluation of polyclonal intravenous immunoglobulin adjunctive therapy in the 3 scenarios defined by the panellists.

Description of scenario: Patient admitted to hospital after < 24 hours from the onset of symptoms with rapid worsening of acute respiratory failure (PaO₂/FiO₂ <200 mmHg) from SARS-CoV2 related interstitial pneumonia and high plasma levels of inflammatory parameters as C-reactive protein, Ferritin and IL-6.

Questions:

1) In COVID-19 patients with acute respiratory failure and severe hyperinflammatory response how appropriate is the early (within 6-12 hours) therapy with polyclonal intravenous immunoglobulins?

Consensus Rating: Uncertain; median score 6 (IQR 5-7); Disagreement: YES

2) In COVID-19 patients with acute respiratory failure, severe hyperinflammatory response and decision to use polyclonal intravenous immunoglobulins how appropriate is the use of preparation including also IgM component?

Consensus Rating: Appropriate; median score 8 (IQR 6-9); Disagreement: NO

Rationale:

In the early phases of COVID-19, the pro-inflammatory response often predominates with the massive production of proinflammatory cytokines such as tumour necrosis factor (TNF)- α , IL-8 and IL-6 that stimulate the effector functions of neutrophils, macrophages and Th1 cells. This dysregulated inflammatory response is similar to that observed in the early phase of sepsis, especially in conditions leading to toxic shock syndrome as pneumococcal and meningococcal invasive disease or necrotizing fasciitis [48]. In this setting, a potential benefit from the early use of adjunctive therapy with IVIg, particularly of IgM enriched preparation, has been shown in numerous clinical experiences [49–51] and its use is supported by many experts, despite the lack of definitive evidence. As described above, the rationale for IVIg administration in patients with a high inflammatory response is based on their immunomodulating effects. A recent phase II trial showed that in patients with severe community-acquired pneumonia requiring mechanical ventilation and with a high inflammatory pattern, the adjunctive therapy with a new intravenous immunoglobulin preparation containing 18% of IgM reduced the mortality by about 20% compared to placebo [52]. Two-phase III trials in community-acquired pneumonia and COVID19 patients are underway to confirm the results observed with the use of this new preparation. In septic patients with hyper inflammation or toxic shock, the timing for IVIg therapy may have a substantial role and 2 large studies indicated that an earlier therapy (within 12 hours) may decrease the mortality risk [49].

SCENARIO 2, LATE PHASE: COVID-19 interstitial pneumonia and suspected immune-dysfunction / immune-paralysis

Description of scenario: Patient requiring mechanical ventilation for progressive worsening of acute respiratory failure several days (7-10) after the occurrence of COVID19 interstitial pneumonia and with low plasma levels of inflammatory parameters as C-reactive protein, Ferritin and IL-6 and persistent lymphopenia.

Questions:

1) In COVID-19 with progressive worsening of respiratory failure, suspected immune-dysfunction/immune-paralysis and low plasma levels of immunoglobulins, how is appropriate the replacement therapy with polyclonal intravenous immunoglobulins to prevent secondary infections?

Consensus Rating: Appropriate; median score 7 (IQR 6-8); Disagreement: NO

2) In COVID-19 with progressive worsening of respiratory failure, suspected immune-dysfunction/immune-paralysis and with the decision to use polyclonal intravenous immunoglobulins, how is appropriate the use of preparation including also IgM component?

Consensus Rating: Appropriate; median score 8 (IQR 7-8); Disagreement: NO

Rationale:

In COVID-19 patients, the anti-inflammatory response, mediated by molecules such as IL-10, IL-4 and TGF- β , is finalized to balance the initial pro-inflammatory response described in several models. Therefore, as previously described, in COVID-19 patients several alterations in innate and adaptive immunity occur, including marked lymphopenia. However, a dysregulated and/or persistent activation of the anti-inflammatory components, often with the addition of anti-inflammatory treatments (eg: steroids, cytokine-blocking agents and others), may cause a severe failure of the immune system defined in sepsis models as immune paralysis and characterized by

lymphopenia with marked T cell exhaustion, alteration of cytokines profile, the inadequacy of antigen-presenting mechanisms and dysfunction and apoptosis of B and T lymphocytes [16,21]. Patients with immune paralysis are unable to mount an appropriate inflammatory response and become prone to viral reactivation and secondary or breakthrough infections mostly by opportunistic agents. A high rate of secondary bacterial and viral infections have been reported by numerous studies in COVID19 patients, especially in those requiring mechanical ventilation and ICU admission [53,54].

In patients with sepsis, low plasma levels of Ig have been frequently reported and are closely related to the severity of the underlying conditions and poor outcome [55]. Moreover, the kinetics of plasma IgM in the first days after sepsis is different in survivors and non-survivors of septic shock [30]. In an observational study involving 62 COVID19 patients with ARDS admitted to ICU [56], the authors observed that in patients with IgG levels below 7 g/L the 90-day mortality was larger than in patients whose levels exceeded 7g/L.

In immune-compromised patients, IVIg therapy is commonly used for preventing infections and sepsis [34,35]. In patients with hypogammaglobulinemia after heart transplantation, IgG prophylactic therapy decreased the incidence of severe secondary infections but the same signal was not observed after lung transplantation [57,58]. Indeed, a more recent metanalysis showed that the prophylactic use of IVIg therapy was associated with a better survival rate in heart and lung recipients with hypogammaglobulinemia [59].

SCENARIO 3, SEPSIS BY BACTERIAL SUPERINFECTION: COVID-19 interstitial pneumonia with septic shock by hospital-acquired superinfection.

Description of scenario: Patient with acute respiratory failure by COVID19 interstitial pneumonia and occurrence of septic shock sustained by nosocomial bacterial infection.

Questions:

1) In COVID-19 patients with septic shock due to nosocomial acquired infections, how appropriate is the adjunctive therapy with polyclonal intravenous immunoglobulins?

Consensus Rating: Appropriate; median score 7 (IQR 6-8); Disagreement: YES

2) In COVID-19 patients with septic shock due to nosocomial acquired infections with the decision to use adjunctive therapy with polyclonal intravenous immunoglobulins, how appropriate is the use of preparation including IgM component?

Consensus Rating: Appropriate; median score 9 (IQR 8-9); Disagreement: NO

Rationale:

Critically ill COVID19 patients are prone to secondary infections because of many factors as invasive mechanical ventilation, long ICU stay, anti-inflammatory therapies, SARS-CoV19 induced immune suppression. Worldwide studies reported a high rate of ventilator-associated pneumonia ranging from 23% to 37%, and secondary bacteraemia in ICU admitted patients. In addition, as for other categories of complicated ICU patients, infections from multidrug-resistant bacteria or *Aspergillus* spp. are frequent in COVID19 patients [53,60–62]. Therefore, sepsis and septic shock often complicate the ICU stay and are a major cause of mortality [63–65]. Despite the lack of definitive evidence, IVIg adjunctive therapy has been used for 30 years and metanalysis indicate a possible benefit in septic patients, with better results by using preparation enriched with IgM component [48,51]. Many authors support adjunctive therapy in specific phenotypes of septic patients as those with hyper inflammation, overwhelming shock or blunted inflammatory response [66]. Indeed, most clinical experiences refer to the former phenotypes while the data in immunocompromised septic patients are scarce and not definitive. The use of IgM preparation has been also demonstrated effective in ICU patients with MDR infections, particularly by gram-negative microorganisms [30,48].

CONCLUSIONS

The alterations in immune and inflammatory response observed in the different phases of COVID19 are similar to those observed in septic patients. The key role of endogenous immunoglobulins in host response and the large experience in immunocompromised and in septic patients make adjunctive therapy with IVIg attractive in COVID19, particularly in hospitalized patients with severe respiratory failure. Despite the paucity of data existing, the structured consensus identified a rationale in the use of IVIg therapy in these patients with immune-paralysis for preventing secondary infections and in patients with septic shock caused by nosocomial infections. Several appropriate studies are underway (ClinicalTrials.gov Identifier: NCT04432324, NCT04500067, NCT04576728, NCT04350580, NCT04350580) for defining, the patient who can benefit the most and the appropriate time and dose of IVIg therapy.

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Author's contribution: Conceptualization, CI, BS, GM, DRF, TC; Methodology CI; Writing – Original Draft Preparation CI, BS, GM; Writing – Review BG, DRF, DA, FF, GG, ML, TC, VP

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