Retrospective Study
Delayed inflammatory pulmonary syndrome - a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection?

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Abstract

BACKGROUND
During the second wave of the COVID-19 pandemic, a subset of critically ill patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction.

AIM
We sought to describe the clinical and laboratory characteristics, outcomes, and management of these patients, and to contrast this entity with other post COVID-19 immune dysregulation related inflammatory disorders.

METHODS
This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO₂/FiO₂ (PF) ratio and levels of inflammatory markers before
and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

RESULTS
Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction at a median (interquartile range, IQR) duration of 32 (23-35) days after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) days, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

CONCLUSION
This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation appears to contrast the well described Multisystem Inflammatory Syndrome - Adults (MIS-A) by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like c-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

INTRODUCTION
While much has been written about COVID-19-Associated Acute Respiratory Distress Syndrome (CARDS) [1], less is known about the clinical presentations that evolve after the acute infection has subsided. The Centre for Disease Control (CDC) has grouped a cluster of organ failure syndromes under the umbrella of multi-system inflammatory syndrome (MIS). This entity is characterised by dysregulated host immune response
causing widespread organ dysfunction and usually follows the period of viremia [2]. MIS was first described in COVID-19 in the paediatric population and was termed MIS-C (Children) [2]. Although a similar phenomenon was subsequently reported in adults (MIS-A) in 2021 [3], the MIS-A criteria, in contrast to the MIS-C, is strikingly bereft of respiratory involvement. It has encompassed primarily an extrapulmonary syndrome with cardiac, neurologic, and gastrointestinal manifestations [3].

While managing COVID-19 patients in the intensive care unit (ICU), we observed that a small subset of patients with CARDS developed worsening respiratory function after an initial period of improvement that could not be attributed to the usual causes such as superadded infection, lung collapse, pleural effusion, pulmonary embolism, or fluid overload. Unlike CARDS or the fibrotic phase of ARDS which are a continuum of the initial insult, this phenomenon was observed in patients with increasing ventilatory requirements between the third and fourth weeks after the diagnosis of COVID-19. Respiratory deterioration was associated with an increase in inflammatory markers with minimal or no extrapulmonary organ involvement. This clinical picture suggested an entity not fitting into the classical MIS-A definition but nevertheless befitting a distinct position in the spectrum of inflammatory syndromes in COVID-19.

The study was thus aimed to describe the clinical and laboratory characteristics of this delayed inflammatory pulmonary syndrome (DIPS) through a retrospective review of cases admitted in the ICU during the second wave of the pandemic, along with clinical outcomes and caveats in management.

**MATERIALS AND METHODS**

*Study setting and design:* This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021.
Study approval: The study was approved by the Institutional Review Board of the institution. In view of the retrospective nature of the study and the large number of COVID-19 patients admitted in the ICU, informed consent waiver was obtained from the institutional review board.

Data harvesting: Computerised records of patients admitted in the medical ICU during the period of study was accessed and those fulfilling the following diagnostic criteria for delayed inflammatory pulmonary syndrome were included in the analysis.

Criteria for the diagnosis of delayed inflammatory pulmonary syndrome (modified from CDC criteria for MIS-C): Patients were considered to have DIPS if they fulfilled ALL the following clinical and laboratory criteria.

Clinical Criteria: Documented fever (≥38.0°C) along with evidence of respiratory involvement in the form of:

Development of respiratory failure or worsening respiratory failure following a period of initial improvement, occurring after the third week of COVID illness and requiring either non-invasive or invasive mechanical ventilation, with documented acute drop in PaO₂/FiO₂ (PF) ratio, resulting in a change in the respiratory SOFA score by at least one point over 24 h.

New or worsening bilateral diffuse infiltrates on chest radiograph or computed tomography (CT) scan, not due to pleural effusion, lobal collapse, pulmonary nodules, or pulmonary embolism.

Respiratory failure not explained by left atrial hypertension or cardiac failure or fluid overload.

Exclusion of infection as the cause of worsening lung function.

Laboratory evidence: The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.
Elevated levels (exceeding the upper limit of normal specific to age and gender) of at least **TWO** of the following: C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), or erythrocyte sedimentation rate (ESR).

A positive SARS-CoV2 test by reverse transcriptase polymerase chain reaction (RT-PCR), serology, or antigen detection in the current admission or in the previous 12 wk [3].

Negative blood culture and endotracheal aspirate cultures collected at the time of worsening of lung function and not fulfilling the CDC definition of ventilator associated pneumonia (VAP) [4].

**Management protocol:** Adult patients aged ≥ 18 years fulfilling criteria for CARDS received as part of the protocol, dexamethasone 6 mg once daily for 10 days and therapeutic anticoagulation if D-Dimer was more than 1000 ng/mL. Following the diagnosis of DIPS, patients were treated with intravenous immunoglobulins (IVIG) at a dose of 2 g/kg over three to five days, or with steroids (6 mg dexamethasone once or twice daily or hydrocortisone 50 mg every six hours, as per the treating clinician’s assessment and discretion). The decision on the use of IVIG was left to the treating physician and also guided by financial feasibility. Daily clinical monitoring and blood gas analysis was done to track improvement in respiratory function.

**Statistical analysis:** The data was tabulated and analysed using Microsoft Excel version Office 365. Continuous variables were presented as mean (standard deviation, SD) for normally distributed data and as median (interquartile range, IQR) for skewed data. Categorical data were reported as proportions. Paired-t test was done to analyse the change in PF ratio before and after the onset of DIPS.

**Main outcomes and measures:** The outcome measures that were assessed were survival to discharge, change in the PF from the onset of DIPS to after immunomodulation, change in inflammatory markers before and after DIPS and duration of mechanical ventilation after the onset of DIPS.

**RESULTS**
Five patients, with mean (SD) age of 48.2 (14.2) years and median (IQR) Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score of 19 (IQR 10-21), fulfilled the case definition of DIPS. One patient who was included had a positive endotracheal aspirate culture (patient 4) but did not fulfil the CDC criteria for VAP [4]. All five patients underwent point of care echocardiography for assessment of left ventricular function. There was no evidence of left ventricular dysfunction; in addition, 3 of the 5 patients in whom an NT pro-BNP was done had values of 449, 132 and 146 pg/mL (reference range: up to 125 pg/mL). There was a male preponderance (80%); the lag time from symptom onset to deterioration was a median 32 days (IQR 23-35 days). One patient (patient 2) had received 2 doses of vaccination with the Oxford-AstraZeneca ChAdOx1 nCoV-19 recombinant vector Corona Virus Vaccine (Brand: Covishield™, manufactured by the Serum Institute, India) prior to admission. Two patients (patients 3 and 5) were not vaccinated. The vaccination history of the remaining two patients (patient 1 and 4) could not be ascertained as contact could not be established through telephone.

Clinical and laboratory characteristics at baseline and at the time of respiratory deterioration are summarised in Table 1. Figure 1 illustrates that respiratory SOFA scores contributed predominantly to the total SOFA score in all subjects on the day of deterioration. Representative chest radiographs and high-resolution computed tomography (CT) scan images taken before the onset of symptoms, at the nadir of PF ratio and during recovery show the evolution of diffuse infiltrates and resolution following treatment (Figure 2).

There was a significant drop in the PF ratio from a peak of 323 ± 96.2 (mean ± SD) prior to DIPS to 169.8 ± 33.7 (mean ± SD) after the onset of DIPS (P = 0.043). There was an increase in the levels of inflammatory markers (CRP, Ferritin) at the onset of DIPS when compared with baseline (Table 1); IL-6 Levels were also elevated (Table 1). The median duration of mechanical ventilation prior to the onset of DIPS was 9 (2-16) days.

At the time of deterioration of respiratory function, of the 5 patients, two patients (patients 2 and 4) deteriorated while on a spontaneous mode of invasive ventilation to
require high ventilatory support. Both these patients were subsequently weaned off the ventilator following immunomodulation and extubated; at the time of discharge, they were on room air. Two other patients (patients 1 and 3) were on intermittent non-invasive ventilation (NIV) at the time of deterioration, worsening to require continuous NIV with increased oxygen support and higher positive end-expiratory pressure (PEEP). Following immunomodulation, patient 3 improved and was discharged stable while patient 1 developed a tension pneumothorax, and subsequently a nosocomial infection and succumbed. Patient 5 who was initially admitted for moderate COVID-19 infection and discharged home re-presented on day 36 with worsening respiratory failure needing intubation and mechanical ventilation. She improved with immunomodulation and was discharged stable.

All 5 patients were on anticoagulation at the time of respiratory deterioration. Of these, 2 were on therapeutic anticoagulation with low molecular weight heparin (enoxaparin) at a dose of 1 mg/kg every 12 h (monitoring of anti-factor Xa levels was done on one patient) while the other 3 patients were on unfractionated heparin with monitoring of activated partial thromboplastin time (APTT).

Following the diagnosis of DIPS, two patients received IVIG at 2 g/kg over 5 days, while one received dexamethasone at 6 mg twice daily for 5 days followed by once daily for 5 days, one received dexamethasone 6 mg once daily for 10 days, and the fifth received hydrocortisone 50 mg every six hours for 5 days. Following immunomodulation there was a significant improvement in the PF ratio from 169.8 ± 33.7 at the onset of DIPS to 349.2 ± 57.6 (P = 0.001) over time. The trends of PF ratios over time for the 5 individual patients is shown in Figure 3. Mechanical ventilation was required for a median duration of 13 (10-23) days after the onset of DIPS. Four out of the five patients (80%) survived to hospital discharge.

**DISCUSSION**

This series describes five critically ill patients with CARDS who developed unexplained worsening respiratory function after a median interval of 32 days (IQR 23-35 days) from
the onset of symptoms of COVID-19. These patients had increased inflammatory markers and responded to immunomodulation. This syndrome of worsening gas exchange appears to be part of a dysregulated host immune response; however, the clinical characteristics of our subset of patients did not fit in to criteria described for the diagnosis of MIS-A.

Lung hyperinflammation is an established phenomenon in the context of CARDS and occurs as part of the initial presentation of COVID-19 infection, generally in the second week following onset of symptoms. Our novel observation of ventilated CARDS patients developing delayed pulmonary hyperinflammation three to four weeks after the onset of initial symptoms, which improved with immunomodulation, has hitherto not been reported.

In a large cohort of MIS-A, patients developed MIS-A at a median time of 28 days from the onset of COVID-19-like illness. The time of presentation in our cohort was similar (median 32 days). However, the paucity of extrapulmonary organ dysfunction and the predominance of lung involvement sets it apart from MIS-A cohorts. It is unclear if DIPS represents a distinct clinical entity or is part of the spectrum of MIS-A. The differences between DIPS, CARDS and MIS-A are summarised in Table 2.

Deteriorating lung function occurring beyond 4 wk after COVID-19 illness, in the absence extra-pulmonary organ involvement has also been previously reported from a few centres either as persistent post COVID-19 interstitial lung disease (ILD), organising pneumonia (OP), secondary organising pneumonia or pulmonary fibrosis. Although the time of onset of symptoms may imply a similar pathology in our cohort, there are several differences that merit consideration. All the 35 patients described in the ILD case series were reviewed 4-weeks after discharge following a telephone interview, in the outpatient clinic, for persistence of respiratory symptoms. In another report, two patients presented two months after discharge: one with new onset breathlessness for 3 days and the other with a 1-week history of worsening cough and right sided pleuritic chest pain. The case report of a 36-year-old male with diffuse
large B-cell lymphoma [8] was an acute presentation with high fever and fatigue, 40 days after a COVID infection. All the patients described in these publications were discharged from hospital after the initial illness and on review reported persistence of respiratory symptoms [7,9] or presented with new symptoms after recovery [8] that were not severe enough to warrant ventilatory support. In contrast, all the patients in our cohort barring one, developed worsening symptoms while in hospital, occurring as a continuum after the initial improvement following treatment for CARDs, were much sicker, and required ventilatory support. The radiological features in the reports [7-9] ranged from focal consolidation, ground-glass attenuation, and linear opacities [7] to extensive pulmonary infiltrates [8] and peri-bronchial and peri-lobar dense consolidation with traction bronchiectasis in the ILD series [9]. In the ILD series, 21 patients with pure ground glass opacities involving <15% of the lung and 3 patients with fixed minor ground glass opacities were excluded and offered follow-up [9]. The patients in our cohort had radiological features of focal or diffuse ground glass opacities in addition to pulmonary infiltrates and tractional bronchiectasis. The radiological features in our series may thus reflect mixed pathology or evolution from one pathological phase of the illness to another, as occurs in ARDS and may not be pathognomonic of a specific diagnosis. Although histopathology would have helped characterise the syndrome further, this was not done in our series due to concerns of performing lung biopsy in patients on high ventilatory support. In the other case reports, the histological features were consistent with organising pneumonia [7,8]; biopsy was not done in the ILD series [9].

Pulmonary fibrosis as a cause for clinical deterioration is unlikely in our patients for the following reasons. The rapid deterioration of symptoms correlated with an increase in serum inflammatory markers and imaging (ground glass opacification) that was consistent with an inflammatory process. This clinical picture contrasts the more subacute presentation and imaging characteristics of pulmonary fibrosis of architectural distortion in the form of irregular reticulation, traction bronchiectasis and
honeycombing [14]. The rapid resolution of symptoms and radiological opacities with immunomodulation also makes pulmonary fibrosis less likely.

Other causes for worsening lung function need to be considered. It is possible that prior vaccination could have contributed to ARDS [15]. Vaccination history could not be obtained for all patients and hence association or lack of it could not be ascertained. There is also evidence that microvascular thrombosis contributes to the pathophysiology of COVID-19 infection [16,17]. Although it is possible that microthrombosis may have contributed to the manifestations, worsening of respiratory function cannot be explained only by ongoing thrombosis given that all patients received anticoagulation, and the observation that patients responded rapidly to immunomodulation. However, the debate on the appropriate level of anticoagulation for COVID-19 patients remains unresolved.

The number of patients described in this cohort as well as on persistent post-COVID-19 ILD [9] or post COVID organising pneumonia [8] is small in relation to the proportion of COVID-19 infected patients; however, subsets with varying clinical presentation and course of illness is not unique to COVID-19 and needs to be documented and reported for better understanding of any disease. The response to immunomodulation in our patients highlights the importance of considering this syndrome among the differential diagnosis for delayed respiratory deterioration. Various biomarkers that have been postulated to correlate with increased incidence of the post-acute sequelae of SARS-CoV-2 infection (PASC) are TNF-α, IP-10 (Interferon-inducible protein-10) and IL-6, also need to be explored further [18]. Although larger studies are required to provide additional insights on these preliminary observations, awareness of this clinical entity will help in timely diagnosis and treatment of a potentially lethal cause of respiratory failure in the ICU.

**CONCLUSION**

Delayed inflammatory pulmonary syndrome is a serious and life-threatening complication of long COVID, occurring commonly in the fourth week of illness and
characterised by a predominance of pulmonary hyperinflammation in the absence of secondary infections or fluid overload or extrapulmonary organ system involvement. This entity can be considered in the differential diagnoses in a patient with delayed deterioration in pulmonary function, after a period of initial improvement. The diagnosis is supported by raised inflammatory markers. Treatment with immunomodulation (systemic glucocorticoids or intravenous immunoglobulin) can be considered and a good response expected.

**ARTICLE HIGHLIGHTS**

*Research background*

Delayed deterioration in pulmonary function, following initial improvement, was seen in a subset of patients admitted to the Intensive Care Unit (ICU) during the COVID-19 pandemic. These patients had no evidence of ongoing infection, fluid overload or cardiac dysfunction, but had elevated systemic inflammatory markers. They did not satisfy the diagnostic criteria for Multisystem Inflammatory Syndrome- Adults (MIS-A) due to the paucity of extrapulmonary organ manifestations (mainly cardiac, gastrointestinal and mucocutaneous), but responded well to immunomodulation.

*Research motivation*

Delayed worsening of respiratory function in the ICU is generally attributable to infection, cardiac dysfunction, or fluid overload. But non-infectious inflammatory complications of post COVID-19 immune dysregulation is a distinct clinical entity that may play a role in worsening organ dysfunction in patients who have no evidence of the above.

*Research objectives*

The objectives of the current study were to describe the clinical and laboratory characteristics of post COVID-19 delayed inflammatory pulmonary syndrome (DIPS), the outcomes and management caveats encountered in the management of these
patients, and to contrast DIPS with other post COVID-19 immune dysregulation related inflammatory disorders.

**Research methods**

This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO₂/FiO₂ (PF) ratio and levels of inflammatory markers before and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

**Research results**

Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction at a median (interquartile range, IQR) duration of 32 (23-35) days after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) days, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

**Research conclusions**

This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation appears to contrast the well described Multisystem Inflammatory Syndrome - Adults (MIS-A) by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like c-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a
distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

Research perspectives
Larger prospective studies are required to validate these preliminary observations and formulate treatment guidelines for this inherently reversible entity.

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