



## Growth differentiation factor 15 as an emerging novel biomarker in SARS-CoV-2 infection

Deepak Parchwani, Sagar Dholariya, CDS Katoch, Ragini Singh

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**Deepak Parchwani, Sagar Dholariya, Ragini Singh**, Department of Biochemistry, All India Institute of Medical Sciences, Rajkot 360001, Gujarat, India

**CDS Katoch**, Department of Pulmonary Medicine, All India Institute of Medical Sciences, Rajkot 360001, Gujarat, India

**Corresponding author:** Sagar Dholariya, MD, Assistant Professor, Department of Biochemistry, All India Institute of Medical Sciences, Jamnagar Road, Khandheri, Rajkot 360001, Gujarat, India. [drsagar.dholariya@gmail.com](mailto:drsagar.dholariya@gmail.com)

### Abstract

#### BACKGROUND

Growth differentiation factor (GDF)-15 is a member of a transforming growth factor- $\beta$  cytokine superfamily that regulates metabolism and is released in response to inflammation, hypoxia and tissue injury. It has evolved as one of the most potent cytokines for predicting the severity of infections and inflammatory conditions, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

#### AIM

To investigate the utility of GDF-15 in predicting the severity of SARS-CoV-2 infection.

#### METHODS

PubMed, Reference Citation Analysis, CNKI, and Google Scholar were explored by using related MeSH keywords and data such as the first author's name, study duration, type and place of study, sample size and subgroups of participants if any, serum/plasma GDF-15 level in pg/mL, area under the curve and cut-off value in receiver operating characteristic analysis, method of measurement of GDF-15, and the main conclusion were extracted.

#### RESULTS

In all studies, the baseline GDF-15 level was elevated in SARS-CoV-2-infected patients, and it was significantly associated with severity, hypoxemia, viral load, and worse clinical consequences. In addition, GDF-15 levels were correlated with C-reactive protein, D-dimer, ferritin and procalcitonin, and it had superior discriminatory ability to detect severity and in-hospital mortality of SARS-CoV-2 infection. Hence, GDF-15 might be used to predict the severity and prognosis of hospitalized patients with SARS-CoV-2.

## CONCLUSION

Serial estimation of GDF-15 levels in hospitalized patients with SARS-CoV-2 infection appeared to have useful prognostic value and GDF-15 can be considered a clinically prominent sepsis biomarker for SARS-CoV-2 infection.

**Key Words:** SARS-CoV-2; Growth differentiation factor 15; Biomarker; Risk-stratification; Prognosis

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**Core Tip:** Growth differentiation factor (GDF)-15 levels are higher in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and higher levels are associated with disease severity, viremia and hypoxemia. The consistent increase in the concentration of GDF-15 during a hospital stay is associated with worse outcomes. Hence, serial monitoring of GDF-15 concentrations may provide useful prognostic value for hospitalized patients with SARS-CoV-2. GDF-15 appears to be involved in the underlying pathophysiology, laying the foundation for a novel therapeutic approach for SARS-CoV-2.

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## INTRODUCTION

Coronavirus disease-2019 (COVID-19), an extremely contagious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health problem. The index case of this viral infection was confirmed in Wuhan, the capital city of Hubei Province, China in December 2019[1]. Then, SARS-CoV-2 quickly disseminated across the globe, infecting around 430257564 individuals with a global mortality of 5922047 people as of February 25, 2021[2]. Considering the massive spikes in cases of COVID-19 across countries within a short period of time, the World Health Organization declared COVID-19 as a public health emergency of international concern, giving it a global risk assessment of extremely high[3]. SARS-CoV-2 primarily infects respiratory tract cells and manifests as mild to fatal pneumonitis[4], especially in older men with comorbidities of hypertension, diabetes mellitus, or vascular disease[5].

SARS-CoV-2 is an enveloped virion with positive sense, single-stranded RNA with a genome size of 29.99 kb encoding for multiple nonstructural and structural proteins. The viral envelope contains four anchored structural proteins, spike protein (S), enveloped protein (E), nucleocapsid protein (N) and membrane protein (M)[6]. S glycoprotein (type 1 transmembrane protein) protrudes from the virus surface and embraces two functional components, S1 and S2. S1 helps the virus to bind with host cell through its receptor-binding domain (RBD) and S2 possesses an element essential for SARS-CoV-2 fusion with the host cell membrane[7].

SARS-CoV-2 enters type II pneumocytes in the lungs by binding with membrane-bound angiotensin-converting enzyme (ACE) 2 receptor through its RBD[6], primed by host cell surface transmembrane serine protease-2[8]. SARS-CoV-2 then starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs, resulting in pre-eminent early viral loads and soluble ACE2 (sACE2) protein release into the bloodstream[9]. Cumulative viral load destroys type II alveolar epithelial cells and decreases the synthesis of pulmonary surfactants[10]. Simultaneously, infiltration of macrophages causes secretion of various cytokines namely tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 and IL-6, instigating migration of lymphocytes and neutrophils and vasodilatation. This dysregulated host immune response plays a crucial role in the pathogenesis of the cytokine storm in SARS-CoV-2 infection[11].

Common clinical manifestations of SARS-CoV-2 infection are pyrexia, tussis, dyspnea, pharyngitis, myalgia, headache, and olfactory and taste dysfunction (hyposmia/anosmia or ageusia)[12]. However, severe consequences such as viral sepsis have been observed in approximately 20% of SARS-CoV-2-infected patients. Sepsis is a life-threatening systemic condition that graduates to cytokine storm followed by immune dysregulation, leading to systemic hyperinflammatory state, acute respiratory distress syndrome (ARDS), multiorgan failure, and development of sepsis-related complications with increased mortality[13].

Apart from inflammation and virulence, tissue tolerance and host response are also important factors for the pathogenesis and resultant consequences of SARS-CoV-2 infection[14]. A member of the transforming growth factor- $\beta$  superfamily, growth and differentiation factor (GDF)-15, is a multifunctional anti-inflammatory cytokine that increases immunotolerance physiologically. It is an evolving modulator of immune responses and facilitates inflammation-induced tissue tolerance through metabolic adaptation[15,16]. Various pathways such as inflammation, hypoxia and oxidative stress tightly regulate expression of GDF-15[17]. In an animal model infected by human rhinovirus, GDF-15 promotes viral replication and virus-induced inflammation in the lungs[18]. Thus, GDF-15 may attenuate the antiviral immune response and affect the consequences of SARS-CoV-2 infection. Conversely, GDF-15 might increase in SARS-CoV-2 infection due to the altered balance of proinflammatory and anti-inflammatory cytokines[14].

Some biomarkers, such as C-reactive protein (CRP), D-dimer, ferritin[19] and presepsin[20], have been identified as biomarkers to assess the inflammation and consequences of SARS-CoV-2 infection. However, more than a year into the pandemic with little evidence of specific therapeutic regimens, front-line clinicians are still reliant on clinical presentation and basic imaging facilities for assessing risk stratification of SARS-CoV-2[21]. Since there are limited data on the accuracy of laboratory investigations for evaluating the severity of SARS-CoV-2 infection[22], identifying a novel biomarker such as GDF-15 offers the opportunity to triage patients for disease severity, allowing better care and timely management of critical patients. As GDF-15 predicts tissue tolerance in SARS-CoV-2-induced inflammation[14], it is worth reviewing the importance of GDF-15 for diagnosis and risk stratification of SARS-CoV-2. This systematic review emphasizes the importance of GDF-15 in SARS-CoV-2 infection by providing the most current evidence from studies that have examined GDF-15 in SARS-CoV-2 patients.

## MATERIALS AND METHODS

### *Literature search strategy*

The highly sensitive systematic literature search was carried out in multiple electronic databases: PubMed, Reference Citation Analysis (RCA), China National Knowledge Infrastructure (CNKI), Web of Science and Google Scholar. The following MeSH keywords were used to search the literature: GDF-15 AND SARS-CoV-2 OR GDF-15 AND COVID-19 OR GDF-15 AND 2019-nCoV OR GDF-15 AND Coronavirus Disease 2019. The inclusion criteria were English language articles published between December 1, 2020 and February 15, 2022. The original research articles, case series, brief reports, and letters were accepted for review. All selected articles' reference list was further screened to identify additional possible research literature. There was no exclusion based on the study outcome and stage or severity of SARS-CoV-2 infection. Finally, seven out of 24 articles were selected for the review after removing the duplicate research literature.

### *Data extraction*

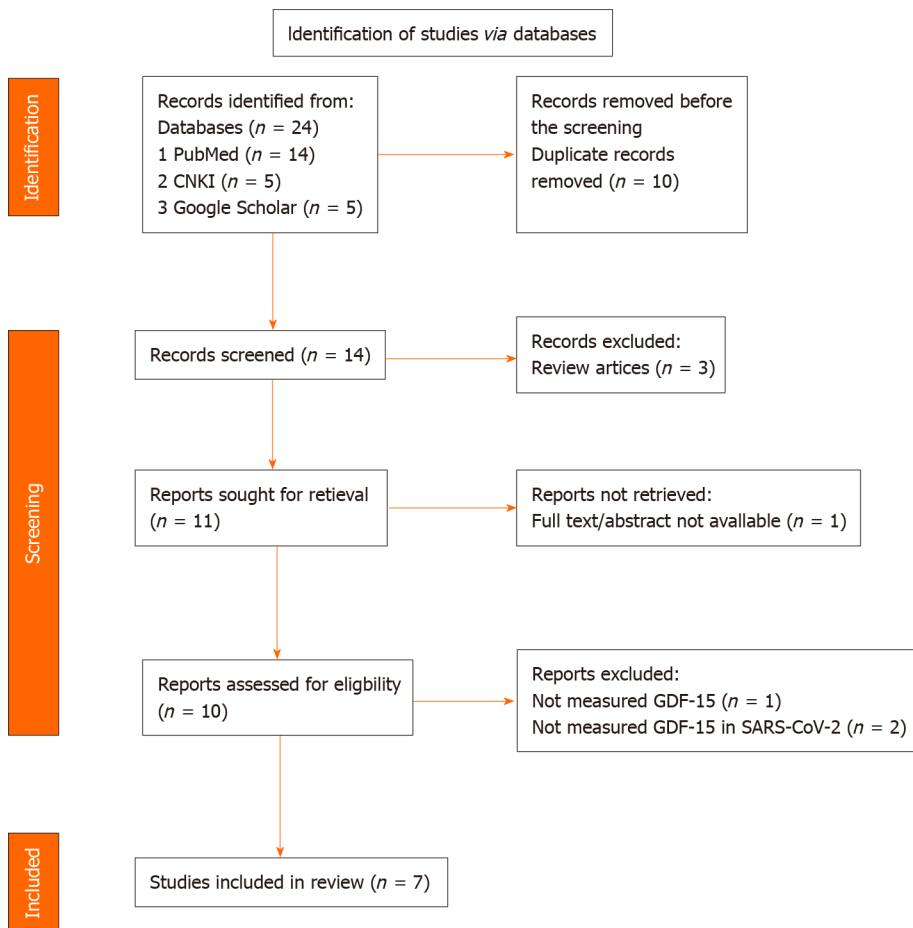
Using the above key terms, the first two authors independently searched for research literature following the inclusion and exclusion criteria, and both authors selected the final articles. The data were extracted in duplicate by standardized data extraction tables by two researchers. The following data were extracted: first author, place of study, sample size, disease severity/stage, intensive care unit (ICU) admission, survivors and nonsurvivors/death, GDF-15 level, and correlation with other inflammatory or sepsis biomarkers.

## RESULTS

A total of 14 studies were retrieved after removing the duplicate or repeated publications; 13 of which were evaluated in full text. Among the included studies, seven were considered suitable for the qualitative synthesis. The process flow for the extraction of research literature (Figure 1) was conducted according to the guidelines defined in the PRISMA statement 2020 and was performed in accordance with a predetermined published protocol (PROSPERO ID: CRD42022311838).

## DISCUSSION

The primary analysis of this systematic review revealed a high level of GDF-15 in SARS-CoV-2-infected patients and found a significant interaction with the severity of COVID-19. GDF-15 was also found to be positively correlated to predict the disease severity and to some degree is worthier than other inflammatory biomarkers as CRP, D-dimer, procalcitonin and ferritin. This conclusion came firstly from the study by Myhre and colleagues in 2020, which evaluated the utility of serum GDF-15 as a prognostic biomarker in hospitalized patients with SARS-CoV-2, and compared it with other known inflammatory



**Figure 1** Flow diagram for selection of research studies from various databases according to PRISMA 2020 guidelines. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

biomarkers (CRP, D-dimer, IL-6, procalcitonin and ferritin) in the Norwegian population from March 18, 2020 to May 4, 2020. The baseline GDF-15 level was elevated in 78% of cases of SARS-CoV-2 infection and it was found to be associated with viral load and hypoxemia. The GDF-15 concentrations were higher in patients who met the primary endpoint of ICU admission or death [4225.0 (3197.0–5972.0) pg/mL *vs* 2187.0 (1344–3620.0) pg/mL,  $P < 0.001$ ]. Patients who reached the primary endpoint had a significant rise in GDF-15 from baseline to day 3 [86.0 (322.0–491.0) *vs* 1208.0 (0–4305.0) pg/mL,  $P < 0.001$ ]. The area under the receiver operating characteristic curve (ROC) was 0.78 (95% confidence interval = 0.70–0.86), indicating a better prognostic significance of GDF-15 than for recognized inflammatory biomarkers such as CRP, ferritin, procalcitonin and IL-6. They derived a cut-off value of 2252.0 pg/mL that differentiated non-ICU survivors from nonsurvivors or ICU admission with good accuracy [23].

Secondly, Notz *et al* [24] measured blood GDF-15 in patients with SARS-CoV-2-induced ARDS in the German population from March 14 to May 28, 2020 and reported an increased level of GDF-15 in patients during their ICU stay. In addition, they testified that comorbidities were unlikely to influence the blood GDF-15 levels, and GDF-15 was not correlated with age, BMI or other anthropometric variables of patients [24]. Subsequently, Luis García de Guadiana Romualdo *et al* [25] evaluated the effect of circulating GDF-15 levels to predict the mortality of hospitalized SARS-CoV-2-infected patients in the Swedish population from March 14 to April 12, 2020. They found a significantly elevated level of GDF-15 in nonsurvivors compared to survivors of SARS-CoV-2 infection [9448.0 (6462.0–11707.0) *vs* 2590.0 (1886.0–4811.0) pg/mL]; a superior discriminatory ability of GDF-15 to predict in-hospital mortality at the cut-off value  $\geq 7789.0$  pg/mL [AUC = 0.892 (0.792–0.955),  $P < 0.001$ ]. GDF-15 levels were also positively correlated with CRP ( $r = 0.527$ ;  $P < 0.001$ ), ferritin ( $r = 0.334$ ;  $P = 0.006$ ) and D-dimer ( $r = 0.260$ ;  $P = 0.035$ ). They concluded that GDF-15 might be used to predict the prognosis of in-hospitalized patients with SARS-CoV-2 [25].

Likewise, Teng *et al* [26] retrospectively evaluated the profile of inflammatory factors in SARS-CoV-2-infected patients and healthy controls in China from January 22 to May 13, 2020. They assessed GDF-15 by categorizing SARS-CoV-2 patients into asymptomatic, mild, moderate, severe and convalescent; GDF-15 at admission, remission and discharge to find the association between dynamic alteration in



GDF-15 with the progression of SARS-CoV-2 infection, and found that GDF-15 concentration escalated consistently with disease severity. GDF-15 expression returned to normal in the convalescent group, as it did in the healthy participants. In continuance, study data revealed GDF-15 levels acutely upsurged with the worsening of symptoms before death, inferring that GDF-15 aptly monitors progression of SARS-CoV-2 infection. They reported an AUC value of 0.89 for GDF-15, which implied that the serum GDF-15 is an effective diagnostic biomarker to assess the severity of SARS-CoV-2 infection[26].

A prospective study conducted in the Swedish population[27] to evaluate the GDF-15 in SARS-CoV-2-infected patients and healthy controls reported a significantly ( $P < 0.001$ ) higher level of GDF-15 in the severe [3562.0 pg/mL (2458.0–5880.0)] and moderate [3450.0 pg/mL (2337.0–4105.0)] type of SARS-CoV-2 infection compared to mild infection [748.0 pg/mL (586.0–1087.0)] and healthy participants [703.0 pg/mL (501.0–949.0)] throughout the acute phase. In the follow-up visit at 6 mo, severe and moderate SARS-CoV-2 infection was recorded with a high GDF-15 level compared to mild type and healthy controls ( $P < 0.05$ ). Like the findings of Myhre *et al*[23], these authors also reported a significant association of GDF-15 with hypoxemia, viral load, and worse clinical consequences in SARS-CoV-2 infection[27].

Ebihara *et al*[28] conducted a prospective, multicenter observational study in the Japanese population to evaluate the role of cytokines in the pathogenesis of SARS-CoV-2 infection, through proteomics analysis. They found: an increased level of GDF-15 in patients with SARS-CoV-2 infection during ICU stay; an AUC of 0.764 and 0.740 for SARS-CoV-2 infection severity and prognosis, respectively; plasma level of GDF-15 was significantly associated with the time to wean off mechanical ventilation and delay recovery in ICU. Based on these results, the authors concluded that GDF-15 was positively related to the severity of SARS-CoV-2 infection and its concentration was significantly higher in patients with sepsis compared with SARS-CoV-2 infection[28].

Alserawan *et al*[29] evaluated serum GDF-15 level and correlated it with SARS-CoV-2 infection severity in the Spanish population. They reported a significantly ( $P < 0.0001$ ) higher level of GDF-15 in SARS-CoV-2-infected patients [2051.0 (1474.0–2925.0) pg/mL] compared to healthy controls [582.0 (370.0–807.0) pg/mL] and in patients who were admitted to hospital for  $> 9$  d. They categorized SARS-CoV-2 patients into  $\text{SpO}_2/\text{FiO}_2 \leq 400$  and  $> 400$  to find an association of GDF-15 with lung involvement. They found high GDF-15 levels in SARS-CoV-2-infected patients with  $\text{SpO}_2/\text{FiO}_2 \leq 400$  or lung impairment. GDF-15 concentrations  $\geq 1675.0$  pg/mL were found to be a good predictor for impaired pulmonary function or  $\text{SpO}_2/\text{FiO}_2 \leq 400$  compared with CRP and D-dimer, according to ROC analysis (AUC = 0.729,  $P < 0.002$ )[29]. Wallentin *et al*[30] observed that GDF-15 was associated with SACE2 levels, increased risk of mortality, and cardiovascular disease, which could help identify those at risk for severe COVID-19 infection.

Table 1 abridges the findings of included studies in this systematic review and Table 2 gives an overview of the data pertaining to GDF-15 in the included studies. Gleaned from the included studies, we conclude that GDF-15 has both diagnostic and prognostic importance in SARS-CoV-2 infection. As SARS-CoV-2 invades the lungs, it causes leukocyte migration, endothelialitis, hypoxia and tissue destruction by enhanced innate immunity[31]. All these factors promote secretion of GDF-15 from infected alveolar epithelial cells. Migration of leukocytes releases proinflammatory cytokines such as TNF- $\alpha$ , IL-8, IL-6, IL-1 $\beta$ , interferon- and granulocyte-macrophage colony-stimulating factor, which in turn stimulates the Notch pathway. The Notch pathway may well activate the Wnt and Hippo pathways, which, in succession cause differentiation of IL-17- and GDF-15-mediated inhibition of the T regulatory suppressor cell activity, respectively, which individually and in conjunction with one another results into extreme activation of the immune system. Concurrently, syncytial development further hyperactivates the immune system and results in a cytokine storm. Thus, GDF-15 plays a pivotal role in the immunological context and may influence the pathogenesis of SARS-CoV-2[14,32].

Impaired iron metabolism has also been hypothesized in the development of hyperinflammation and oxidative stress in patients with SARS-CoV-2 infection. GDF-15 has also been found to interact with iron metabolism, hepcidin and erythropoiesis during inflammation. More specifically, elevated GDF-15 during hypoxia and anemia has been found to suppress hepcidin expression, which boosts the iron level for hemoglobin production. As a result, GDF-15 has been considered as an immune modifier to regulate altered erythropoiesis and ferroptosis in patients with SARS-CoV-2 infection with anemia. During inflammation, GDF-15 overexpression has been associated with iron overload, which could increase ferritin, another key biomarker to assess severity of SARS-CoV-2 infection[33]. Hence, this hypothesis supports the association between high GDF-15 and anemia in inflammatory conditions such as SARS-CoV-2 infection, chronic kidney disease[34], diabetes, cardiovascular diseases[35], and cancer[36].

The iron chelation therapy improves innate immunity and endothelialitis in SARS-CoV-2 infection through its antifibrotic and antiviral properties[37] and is substantiated by the fact that the US FDA approved iron chelation therapy as an adjuvant treatment for the management of critical patients with SARS-CoV-2 infection[38]. Consequently, GDF-15 could be considered a crucial biomarker to indicate the prompt use of iron-chelating therapy in SARS-CoV-2 infection.

Metformin has recently been shown to elevate blood GDF15 levels, resulting in decreased satiety and body weight in clinical investigations. In animal studies, metformin was also associated with increased GDF-15 levels, along with increased GDF-15 expression in kidneys and intestines. In addition, metformin supplementation decreased weight in high-fat-fed mice, but not in GDF15-deficient mice and

**Table 1 Studies included in the systematic review, with duration, type, region/place, and main findings**

Refs	Study duration	Type of study	Region/place	Main findings
Myhre <i>et al</i> [23], 2020	March 18, 2020 to May 4, 2020	Prospective, observational study	Norway	GDF-15 has a better prognostic significance than recognized inflammatory biomarkers like CRP, ferritin, procalcitonin, and IL-6
Notz <i>et al</i> [24], 2020	March 14 to May 28, 2020	A single-center retrospective study	Germany	There was no evident imbalance of pro-and anti-inflammatory pathways, with higher GDF-15 levels in patients with SARS-CoV-2 infection during ICU stay, implying elevated tissue resilience
Luis García de Guadiana Romualdo <i>et al</i> [25], 2021	March 14 to April 12, 2020	Case-series	Spain	The GDF level was significantly high in nonsurvivors compared to survivors of SARS-CoV-2 infection, and it may be useful to predict prognosis
Teng <i>et al</i> [26], 2021	January 22, 2020, to May 13, 2020	Retrospective study	China	GDF-15 could be used as a biomarker to predict the severity of SARS-CoV-2 infection. GDF-15 level increased consistently with increased severity of SARS-CoV-2 infection, and GDF-15 expression returned to normal level similarly in a convalescent group compared to the healthy control participants. Hence, it implies that the GDF-15 precisely monitors the progression of SARS-CoV-2 infection
Kanberg <i>et al</i> [27], 2021	February 21 to November 5, 2020	Prospective study	Sweden	Patients with severe and moderate SARS-CoV-2 infection exhibited significantly increased GDF-15 levels compared with participants with mild infection and controls throughout the acute phase. Even after 6 mo of infection, GDF-15 concentrations persisted considerably higher in the severe and moderate infections compared to patients with mild infection and controls
Ebihara <i>et al</i> [28], 2022	August 2020 to December 2020	Prospective multicenter observational study	Japan	GDF-15 may be beneficial to predict delayed recovery or mortality of SARS-CoV-2-infected patients during ICU treatment
Alserawan <i>et al</i> [29], 2021	Not mentioned	Prospective study	Spain	GDF-15 may play a role in categorizing SARS-CoV-2-infected patients based on severity. GDF-15 is an excellent biomarker to detect impaired respiratory function compared to CRP and D-dimer

CRP: C-reactive protein; GDF-15: Growth differentiation factor 15; IL-6: Interleukin 6; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

mice deficient for GFRAL (GDNF family receptor  $\alpha$ -like, receptor for GDF-15) [39-42]. Thus, metformin supplementation has been associated with reduction in mortality in patients with SARS-CoV-2 infection with diabetes.

A few limitations of this analysis should be taken into consideration when interpreting the results for any potential clinical implications. Firstly, the sample size was small. Secondly, heterogeneity was a major issue in the included studies, especially in terms of methodology, type of ongoing treatment, time of sample collection after hospital admission, non-consideration of the disease-onset time and divergence in adjusting study variables (age, gender, and various comorbidities). Thirdly, variance in the quantification of GDF-15 and subclassification of patient populations in the included studies. Lastly, the literature search and coverage were limited to articles published in English; languages other than English were not considered for analysis, which is susceptible to a local literature bias. Nevertheless, the goal of this study was not to create a predictive model but to investigate the potential importance of GDF-15 as a novel biomarker [39-42]. Hence, despite these limitations, this systematic review offers vital information on the risk stratification of SARS-CoV-2, which could in the future become an important part of the clinical process.

## CONCLUSION

GDF-15 appeared to be an important determinant in the etiopathogenesis of disease and might serve as a predictor for onset and severity of SARS-CoV-2 infection. Hence, GDF-15 can be considered a clinically prominent sepsis biomarker for screening, risk stratification, and monitoring SARS-CoV-2.

Table 2 Review of data extracted for growth differentiation factor 15 in SARS-CoV-2 infection from included studies

Refs	Myhre <i>et al</i> [23], 2020	Notz <i>et al</i> [24], 2020	Luis García de Guadiana Romualdo <i>et al</i> [25], 2021	Teng <i>et al</i> [26], 2021	Kanberg <i>et al</i> [27], 2021	Ebihara <i>et al</i> [28], 2022	Alserawan <i>et al</i> [29], 2021
<b>Sample size and subgroup of participants, if any</b>	123 confirmed cases of SARS-CoV-2 infection (non-ICU survivor = 88, ICU admission/ death = 28)	13 cases of SARS-CoV-2 infection with ARDS	66 confirmed cases of SARS-CoV-2 infection (non-survival = 58, survival = 6)	111 confirmed cases of SARS-CoV-2 infection and 20 healthy controls (asymptomatic = 14, mild = 12, moderate = 34, severe = 18, and convalescent = 33)	100 confirmed cases of SARS-CoV-2 infection (mild = 24, moderate = 28, severe = 48) and 51 healthy controls	306 confirmed cases of SARS-CoV-2 infection	84 confirmed cases of SARS-CoV-2 infection and 20 healthy controls
<b>GDF-15 level in pg/mL</b>							
Healthy controls				13.5 (8.0–79.0)	703.0 (501.0–949.0)	-	582.0 (370.0–807.0)
Mild				136.4 (44.7–321.4)	748.0 (586.0–1087.0)	-	2051.0 (1474.0–2925.0)
Moderate		12400.0		256.2 (76.1–341.0)	3450.0 (2337.0–4105.0)	-	
Severe			-	524.8 (405.1–831.1)	3562.0 (2458.0–5880.0)	Increased during ICU stay	
Critical				621.0	-	-	-
Non-ICU survivor	2187.0 (1344.0–3620.0)	-	2590.0 (1886.0–4811.0)	-	-	-	
ICU admission or death	4225.0 (3197.0–5972.0)	-	9448.0 (6462.0–11707.0)	-	-	-	-
<b>AUC and 95% CI of GDF-15 in ROC analysis</b>	0.78 (0.70–0.86) $P < 0.001$	Not mentioned	0.89 (0.792–0.955) $P < 0.001$	0.89	Not mentioned	For severity: 0.764; For prognosis: 0.740	0.729 (0.602–0.857) $P = 0.002$
<b>The optimal cut-off value of GDF-15</b>	2252.0 pg/mL, to differentiate non-ICU survivors and ICU admission or death	Not mentioned	7789.00 pg/mL, to differentiate non-ICU survivors and ICU admission or death	Not mentioned	Not mentioned	Not mentioned	1675.0 pg/mL, to recognize deprived respiratory function ( $\text{SpO}_2/\text{FiO}_2 \leq 400$ )
<b>Method of GDF-15 measurement</b>	ELISA	ELISA	Electro-chemiluminescent	ELISA	Electro-chemiluminescent	ELISA	ELISA
<b>Additional findings related to GDF-15</b>	It was associated with viral load and hypoxemia. Better prognostic significance compared to CRP, ferritin, IL-6, and procalcitonin	It was not correlated with age and BMI	Positively correlated with CRP, ferritin, and D-dimer	GDF-15 indicates the severity and closely monitor the progression of SARS-CoV-2	Elevated GDF-15 was significantly related to hypoxemia, viral load, and worse clinical consequences	The plasma level of GDF-15 was significantly associated with the time to wean-off mechanical ventilation	Positively correlated with CRP, D-dimer, and neutrophil count and negatively correlated with lymphocyte count

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assays; GDF-15: Growth differentiation factor 15; IL-6: Interleukin 6; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

## ARTICLE HIGHLIGHTS

### Research background

Growth differentiation factor (GDF)-15 is a modulator of immune responses and facilitates inflammation-induced tissue tolerance through metabolic adaptation. Experimental studies revealed that GDF-15 promotes virus replication and virus-induced inflammation in the lungs. Thus, GDF-15 may attenuate the antiviral immune response and affect the consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

### Research motivation

To identify a novel biomarker for the guidance of severity of disease, so as to provide better care and timely management of critical patients.

### Research objectives

To investigate the utility of GDF-15 in predicting the risk stratification of SARS-CoV-2.

### Research methods

A systematic literature search was carried out in multiple electronic databases: PubMed, Reference Citation Analysis, China National Knowledge Infrastructure (CNKI), Web of Science and Google Scholar using MeSH keywords. The inclusion criteria were research articles of any type written in the English language and published between December 1, 2020 and February 15, 2022. There was no exclusion based on the study outcome and stage or severity of SARS-CoV-2 infection. Finally, seven of 24 articles were selected for the review after removing the duplicate research literature.

### Research results

The primary analysis of this systematic review revealed a high level of GDF-15 in SARS-CoV-2-infected patients and found a significant interaction with the severity of COVID-19. GDF-15 was also found to be positively correlated to predict the disease severity and is superior to other inflammatory biomarkers such as C-reactive protein, D-dimer, procalcitonin and ferritin.

### Research conclusions

Serial estimation of GDF-15 levels in hospitalized patients with SARS-CoV-2 infection may have useful prognostic value and GDF-15 can be considered a clinically prominent sepsis biomarker for screening, risk stratification, and monitoring SARS-CoV-2.

### Research perspectives

Additional prospective studies are warranted in this regard to justify GDF-15 as an ideal biomarker which should provide optimization of disease status.

## FOOTNOTES

**Author contributions:** Parchwani D and Dholariya S contributed equally to this work from the design of study, search and scrutiny of articles, analysis and manuscript writing to proof reading; Katoch CDS designed the research study, scrutiny of articles and manuscript writing; Singh R literature search and analysis; all authors have read and approve the final manuscript.

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**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2020 Checklist, and the manuscript was prepared and revised according to the PRISMA 2020 guidelines.

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**Country/Territory of origin:** India

**ORCID number:** Deepak Parchwani 0000-0001-5024-970X; Sagar Dholariya 0000-0002-0654-5998.

**S-Editor:** Liu JH

**L-Editor:** Kerr C



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