76138_Auto_Edited.docx

WORD COUNT	3291	TIME SUBMITTED	20-JUL-2022 03:16PM
		PAPER ID	88606683

Name of Journal: *World Journal of Methodology*
Manuscript NO: 76138
Manuscript Type: SYSTEMATIC REVIEWS

Growth Differentiation Factor - 15 (GDF - 15) as an emerging novel Biomarker in SARS-CoV-2 Infection

Deepak Parchwani, Sagar Dholariya, CDS Katoch, Ragini Singh

Abstract

BACKGROUND

Growth differentiation factor 15 (GDF-15), a member of a transforming growth factor (TGF)-β 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 SARS-CoV-2.

AIM

The aim of this systematic review is to investigate the utility of GDF-15 in predicting the severity of SARS-CoV-2.

METHODS

PubMed, CNKI, and Goggle scholar databases 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, AUC and cut-off value in ROC analysis, method of measurement of GDF-15, and the main conclusion were extracted.

RESULTS

Interestingly in all studies, the baseline GDF-15 Level was elevated in SARS-CoV-2 patients, and it was significantly associated with severity, hypoxemia, viral load, and worse clinical consequences. In addition, GDF-15 Levels were correlated with CRP, D-dimer, ferritin, and procalcitonin, and it had superior discrimination ability to detect severity and in-hospital mortality of SARS-CoV-2. Hence, GDF-15 might be used to predict the severity and prognosis of in-hospitalized patients of SARS-CoV-2.

CONCLUSION

GDF-15 Levels are higher in hospitalized patients of SARS-CoV-2, and higher levels are associated with 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 in-hospitalized SARS-CoV-2 patients. GDF appears to be involved in the underlying pathophysiology, laying the foundation for a novel therapeutic approach for SARS-CoV-2.

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 testified in Wuhan, the capital city of the Hubei province of China in December 2019 [1], then SARS-CoV-2 quickly disseminated across the globe, contaminating around 430,257,564 individuals with a global mortality of 5,922,047 people as of February 25, 2021 [2]. Considering the massive spikes in cases of COVID-19 across countries within a short period of time, World Health Organization (WHO) declared COVID-19 as a public health crisis of worldwide importance, 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 elderly males with comorbidities of hypertension, diabetes mellitus, and 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. Viral envelope contains four anchored structural proteins, viz Spike protein (S), Enveloped Protein (E), Nucleocapsid protein (N) and Membrane protein (M)[6]. S glycoprotein (type 1 transmembrane protein) protrudes from virus surface and embraces two functional components, S1 and S2. S1 helps the virus to binds with host cell through its receptor-binding domain (RBD) and S2 possesses an element essential for SARS-CoV-2 fusion with host cell membrane [7].

SARS-CoV-2 virus enters type II pneumocytes of lung by binding with cell membrane bound Angiotensin Converting Enzyme 2 (ACE2) receptor through its RBD [6], primed by host cell surface proteases transmembrane serine protease-2 (TMPRSS2) [8]. SARS-CoV-2 virus then starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs, resulting in preeminent early virus loads and the soluble ACE2 (sACE2) protein release into the bloodstream [9]. Cumulative viral load destroys type II alveolar epithelial cells and diminutions the synthesis of pulmonary surfactants [10]. Simultaneously, infiltration of macrophages causes secretion of various cytokines namely tumor necrosis factor-α (TNF-α), IL-1, and IL-6, instigating migration of lymphocytes, neutrophils and vasodilatation. This dysregulated host immune response plays a crucial role in the pathogenesis of cytokine storms in SARS-CoV-2 infection [11].

Communal clinical manifestations of SARS-CoV-2 infection are pyrexia, tussis, dyspnea, pharyngitis, myalgia, headache, olfactory and taste dysfunction (hyposmia/anosmia or ageusia) [12]. However, severe consequences viz viral sepsis has been observed in approximately 20 percent of SARS-CoV-2 patients. Sepsis is a life-threatening systemic condition that grades to cytokine storm followed by an immune dysregulation, leading to systemic hyper-inflammatory state, acute respiratory distress syndrome (ARDS), multi-organ 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 TGF-β superfamily, Growth and differentiation factor 15 (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 the expression of GDF-15 [17]. In an animal model infected by human rhinovirus, GDF-15 promotes virus replication and virus-induced inflammation in the lungs [18]. Thus, GDF-15 may attenuate the anti-viral 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 pro-inflammatory 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. 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 is limited data on the accuracy of laboratory investigations for evaluating the severity of SARS-CoV-2 [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 systemic 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 systemic literature search was carried out in multiple electronic databases: PubMed, CNKI (China National Knowledge Infrastructure), Web of Science and google scholar databases. The following English MeSH keywords in blends were used to search literature: GDF-15 AND SARS-CoV-2 OR GDF-15 AND COVID-19 OR GDF-15 AND 2019-nCoV OR GDF-15 AND CORONOVIRUS DISEASES 2019. The inclusion criteria were the research literature written in the English language and 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's outcome and stage or severity of the SARS-CoV-2. Finally, 07 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, ICU admission, survivors and non-survivors/death, GDF-15 Level, and correlation with other inflammatory or sepsis biomarkers.

RESULTS

A total of fourteen studies were searched out from the database after removing the duplicate or repeated publications, thirteen 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.

Figure 1 Flow diagram for selection of research studies from various databases according to PRISMA 2020 guidelines

DISCUSSION

The primary analysis of this systematic review revealed a high level of GDF-15 in SARS-CoV-2 patients and undeniably 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 to other inflammatory biomarkers as CRP, D-dimer, procalcitonin, and ferritin. This epilogue emanated; firstly, from the study by Myhre and colleagues in the year 2020, who 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 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 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 to 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 percent CI = 0.70–0.86), indicating a better prognostic significance of GDF-15 than recognized inflammatory biomarkers like CRP and ferritin, procalcitonin and IL-6. They derived a cut-off value of 2252.0 pg/mL that differentiated non-ICU survivors from non-survivors or ICU admission with good accuracy [23].

Secondly, Notz *et al* (2020) [24] measured a blood GDF-15 in SARS-CoV-2 induced acute respiratory distress syndrome (ARDS) patients in the German population from March 14 to May 28, 2020 and reported an increased level with GDF-15 in patients of SARS-CoV-2 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 the age, BMI or other anthropometric variables of patients [24]. Subsequently, Guadiana Romualdo *et al* (2021) [25] evaluated the effect of circulating GDF-15 Levels to predict the mortality of hospitalized SARS-CoV-2 patients in the Swedish population from March 14 to April 12, 2020. They delineated; a significantly elevated level of GDF-15 in non-survivors compared to survivor of SARS-CoV-2 [9448.0 (6462.0-11707.0) vs. 2590.0 (1886.0-4811.0) pg/mL], a superior discrimination ability of GDF-15 to predict in-hospital mortality at the cut-off value of ≥ 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-value < 0.001), ferritin ($r = 0.334$; p-value = 0.006), and D -dimer ($r = 0.260$; p-value = 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 X *et al* (2021) [26] retrospectively evaluated the profile of inflammatory factors in SARS-CoV-2 patients and healthy controls in China from January 22, 2020, 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 and divulged that the GDF-15 concentration escalates consistently with the severity of SARS-CoV-2. 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 the GDF-15 aptly monitors the advancement of the SARS-CoV-2. 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 [26].

A prospective study conducted in the Swedish population [27] to evaluate the GDF-15 in SARS-CoV-2 patients and healthy controls, reported a significant ($p < 0.001$) higher level of GDF-15 in the severe [3562.0 (2458.0–5880.0)] and moderate [3450.0 (2337.0–4105.0)] type of SARS-CoV-2 compared to mild [748.0 (586.0–1087.0)] type and healthy participants [703.0 (501.0–949.0)] throughout the acute phase. In the follow-up visit of 6 mo, severe and moderate SARS-CoV-2 were recorded with a high GDF-15 Level compared to mild type and healthy controls ($p < 0.05$). Like the findings of Myhre PL, *et al* (2020), authors of this study also reported a significant association of GDF-15 with hypoxemia, viral load, and worse clinical consequences in SARS-CoV-2 [27].

Lately, Ebihara *et al* (2022) [28] also conducted a prospective multicentric observational study in the Japanese population to evaluate the role of cytokines in the pathogenesis of SARS-CoV-2 through proteomics analysis. They conveyed; an increased level of GDF-15 in patients of SARS-CoV-2 during ICU stay, an AUC of 0.764 and 0.740 for the SARS-CoV-2 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, authors concluded that GDF-15 was positively related to the severity of SARS-CoV-2 and its concentration was significantly higher in sepsis patients compared to SARS-CoV-2 [28].

Lastly, Alserawan L, *et al* (2021) [29] evaluated serum GDF-15 Level and correlated it with SARS-CoV-2 severity in the Spanish population. They reported a significantly ($p < 0.0001$) higher level of GDF-15 in SARS-CoV-2 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 admitted in the hospital for a long duration (> 9 days). They categorized SARS-CoV-2 patients into SpO2/FiO2 values of ≤ 400 and SpO2/FiO2 values of > 400 to find an association of GDF-15 with lung involvement. Interestingly, they found high GDF-15 Levels in SARS-CoV-2 patients with SpO2/FiO2 values of ≤ 400 or lung impairment. GDF-15 concentrations of ≥ 1675.0 pg/mL were found to be the good predictor for impaired pulmonary function or SpO2/FiO2 ≤ 400 compared to the CRP and D-dimer, according to ROC analysis (AUC = 0.729, $p < 0.002$) [29]. Wallentin L, *et al* (2020) was 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.

Gleaned from the included studies, it is worthwhile to conclude that GDF-15 has both diagnostics and prognostics importance in SARS-CoV-2. Mechanistically, as SARS-CoV-2 virus invades the lungs, it causes leukocytes migrations, endothelialitis, hypoxia and tissue destruction by enhanced innate immunity [31]. All these facets promote the secretion of GDF-15 from infected alveolar epithelial cells. Migration of leucocytes releases pro-inflammatory cytokines namely TNF-α (tumor necrosis factor-alpha), IL (interleukin)-8, IL-6, IL-1β, IFN (interferon) gamma, and GM-CSF (granulocyte monocyte-colony stimulating factor), which in turn stimulates notch pathway. The notch pathway may well activate Wnt and hippo pathway. Hippo and Wnt pathway in succession causes differentiation of IL-17 and GDF-15 mediated inhibition of the T_{reg} suppressors activity respectively, that individually and in conjunction with one another results into extreme activation of immune system. Concurrently, development of syncytium further hyperactivates the immune system results in cytokine storm. Thus, GDF-15 plays pivotal role in the immunological context and may influence the pathogenesis of SARS-CoV-2 [32, 33].

Additionally, the impaired iron metabolism has also been hypothesized for the development of hyperinflammation and oxidative stress in patients with SARS-CoV-2. In the perspectives of iron metabolism, GDF-15 has also been found to be 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 that 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 of SARS-CoV-2 with anemia. Into the bargain, during inflammation, GDF-15 overexpression has been associated with iron overload which could increases ferritin, another key biomarker to assess severity of SARS-CoV-2 [34]. Hence, this hypothesis supports the association between high GDF-15 and anemia in

inflammatory conditions such as SARS-CoV-2, chronic kidney disease [35], diabetes, cardiovascular diseases [36], and cancers [37].

The iron chelation therapy improves innate immunity and endothelialitis in SARS-CoV-2 through its antifibrotic and anti-viral properties [38] and is substantiated by the fact that FDA approved iron chelation therapy as an adjuvant treatment for the management of critical patients of SARS-CoV-2 [39]. Consequently, GDF-15 could be considered a crucial biomarker to indicate the prompt use of iron-chelating therapy in SARS-CoV-2 patients.

Furthermore, metformin has recently been shown to elevate blood GDF15 Levels, resulting in decrease in satiety and body weight in clinical investigations. In animal study, metformin was also associated with increased GDF-15 Levels along with increased GDF-15 expression in kidney and intestine. In addition, metformin supplement cause decreased in weight in high-fat-fed mice, but not in GDF15-deficient mice and GFRAL (GDNF family receptor α-like, receptor for GDF-15)-deficient mice [40-43]. Thus, metformin supplement has been associated with reduction in mortality in patients of SARS-CoV-2 with diabetes.

Limitations

Few limitations of this analysis should be taken into consideration when interpreting the results for any potential clinical implications. Firstly, sample size as to number of studies included for consideration was comparatively smaller. Secondly, heterogeneity is a chief 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 (viz age, gender, and various comorbidities). Thirdly, variance in the quantification of GDF-15 and sub-classification of patient population in the included studies. Lastly, the literature search and coverage were limited to published articles 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 [40-43]. Hence,

despite these limitations, this systemic 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 etiopathogenesis of disease and might serve as a predictor for onset and severity of SARS-CoV-2. Hence, GDF-15 can be considered a clinically prominent sepsis biomarker for screening, risk stratification, and monitoring SARS-CoV-2.

ARTICLE HIGHLIGHTS

Research background

GDF-15 is a modulator of immune responses and facilitates inflammation-induced tissue tolerance through metabolic adaptation. experimental studies reveled that GDF-15 promotes virus replication and virus-induced inflammation in the lungs. Thus, GDF-15 may attenuate the anti-viral immune response and affect the consequences of 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 systemic literature search was carried out in multiple electronic databases: PubMed, CNKI (China National Knowledge Infrastructure), Web of Science and google scholar databases using the relevant MeSH keywords. The inclusion criteria were the research

literature 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's outcome and stage or severity of the SARS-CoV-2. Finally, 07 out 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 patients and undeniably 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 to other inflammatory biomarkers as CRP, D-dimer, procalcitonin, and ferritin.

Research conclusions

Serial estimation of GDF-15 Levels in the SARS-CoV-2 hospitalized patients may provide 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.

76138_Auto_Edited.docx

ORIGINALITY REPORT

7%
SIMILARITY INDEX

PRIMARY SOURCES

1	link.springer.com Internet	91 words — 2%
2	Sagar Dholariya, Deepak N. Parchwani, Ragini Singh, Madhuri Radadiya, C. D. S. Katoch. "Utility of P-SEP, sTREM-1 and suPAR as Novel Sepsis Biomarkers in SARS-CoV-2 Infection", Indian Journal of Clinical Biochemistry, 2021 Crossref	40 words — 1%
3	search.bvsalud.org Internet	21 words — 1%
4	academic.oup.com Internet	20 words — 1%
5	www.nature.com Internet	19 words — 1%
6	journalarticle.ukm.my Internet	14 words — < 1%
7	patents.google.com Internet	13 words — < 1%
8	pure.rug.nl Internet	13 words — < 1%
9	www.esp.org Internet	

13 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS