



Comparative precision and regression analyses of Ferritin with inflammatory biomarkers (PCT, IL-6, D-Dimer, LDH, CRP) from SARS-Covid 19 patients

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Abstract *Background:* Patients of high risk category for developing Covid 19 related complications were identified using several biomarkers such as D-Dimer, Pro-calcitonin (PCT), Ferritin, Interleukin-6 (IL-6), C-reactive protein (CRP), enzymes like Lactate dehydrogenase (LDH) and creatinine kinase, that exhibits correlated elevation as condition of patients progressed critically. Recent and past studies regarding Ferritin as pro-inflammatory marker strongly advocate its diagnostic effectiveness in SARS-Covid 19 infections. *Aim:* Present study described comparative correlation and regression analysis of Ferritin in relation to D-Dimer, CRP, PCT and IL-6 and LDH in critically ill covid-19 patients. *Materials and Methods:* Confirmed and admitted cases of SARS-Covid 19 virus, either in ICUs, HDUs or isolation wards (total 20; 13 males, 07 females) were included in the study by assessing and checking Lab information system (LRS) and files with available and been tested for all six inflammatory biomarkers. Regression correlation analysis was performed using SPSS ver 20.0 (USA) and graphs presented by Y intercept and R², as Ferritin vs IL-6, D-Dimer, LDH, CRP and PCT. *Results:* Regression R² and Y intercept showed Ferritin vs IL-6 as $y = 0.1399x - 90.179$ with R² 0.9507 (Fig 1), vs D-Dimer $Y = 0.0173 x - 11.203$, R² 0.8743 (Fig 2); vs LDH $Y = 1.328 x - 671.61$ R² 0.8955 (Fig 3); vs CRP $Y = 0.017 x - 11.09$ R² 0.8798 (Fig 4); PCT $Y = 0.0174 x - 11.212$ R² 0.8826. *Conclusion:* Data depicts association of compatibility of Ferritin vs IL-6, CRP, PCT, D-Dimer, LDH between 87% to 95%, and thus suggesting high level of credibility of its direct correlation with progression of disease and linear association.

Keywords SARS (Severe acute Respiratory Syndrome), Covid 19, Biomarkers, Inflammatory markers

Short title: Biomarkers correlation in Covid-19 patients

1. Introduction

SARS (Severe acute Respiratory Syndrome)-Covid 19 viral infection, that has emerged from China in 2019, turned into global pandemic of unprecedented proportions and responsible for nearly 88.8 million infected world population and fatality of around 1.91 million [1,2]. Although majority of patients presented with milder symptoms and recovered with conventional treatments, around 10% showed marked respiratory distress and related signs, needed medical assistance and some with intensive care admission [1,3,4]. To identify patients of high risk category for developing Covid 19 related complications, several biomarkers have been employed that showed correlated elevation, as diseased or critical condition of patients progressed or became lower and/or milder when individuals responded well to treatments [1,4-6]. Biomarkers such as D-Dimer, Pro-calcitonin (PCT), Ferritin, Interleukin-6 (IL-



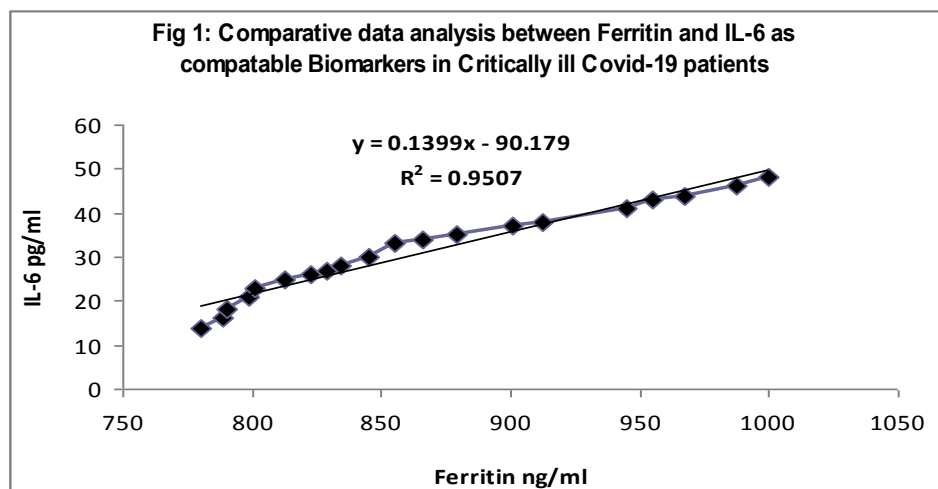
6), C-reactive protein (CRP), enzymes like Lactate dehydrogenase (LDH) and Creatine kinase showed elevation of variable levels for patients with moderate to critical status of SARS-Covid 19 infection [1,4-6]. These biomarkers also indicate disease intensity, progression and/or relatable positive and negative prognosis [7,8]. In this regard, Ferritin, as a major source of iron storage, metabolism, and as Cofactor, provides not only iron storage information but also any untoward effect towards normal metabolic pathways [7-9]. Recent and past studies regarding Ferritin as pro-inflammatory marker strongly advocate its diagnostic effectiveness in SARS-Covid 19 infection [10-13]. Diagnostic efficacy of Ferritin has also been reported for severe pneumonia, haemophagocytic lymphohistiocytosis, Lymphopenia or bleeding/coagulation disorders [7,9,10-13] and thus comparative correlation and linear regression became a part of its analytical precision and accuracy since many years [9]. Thus presented study described comparative correlation and regression analysis of Ferritin in relation to D-Dimer, CRP, PCT and IL-6 and LDH in critically ill covid-19 patients.

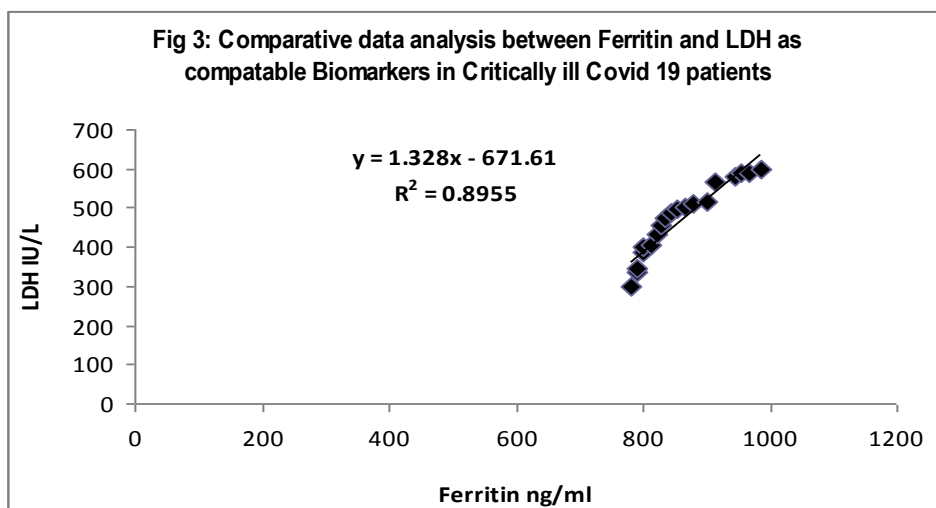
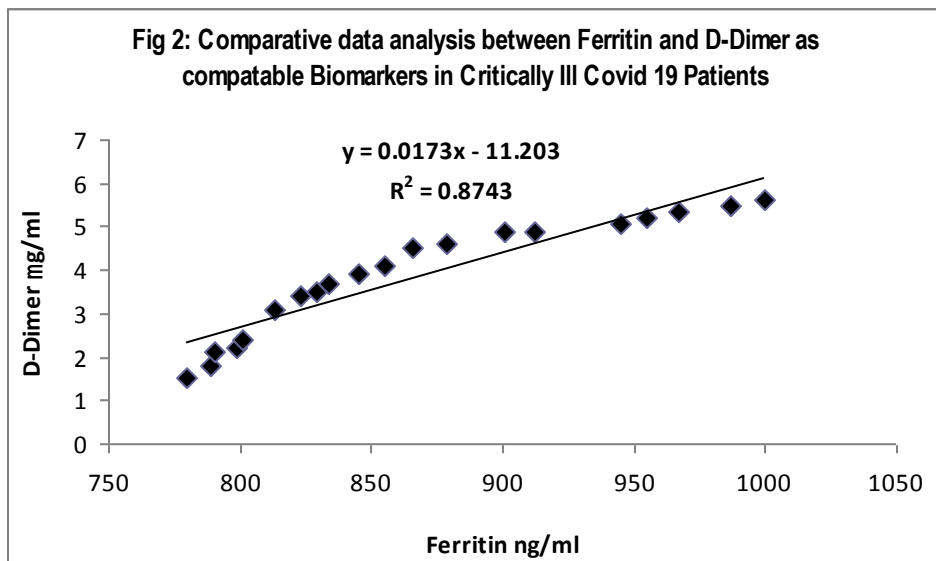
2. Materials and Methods

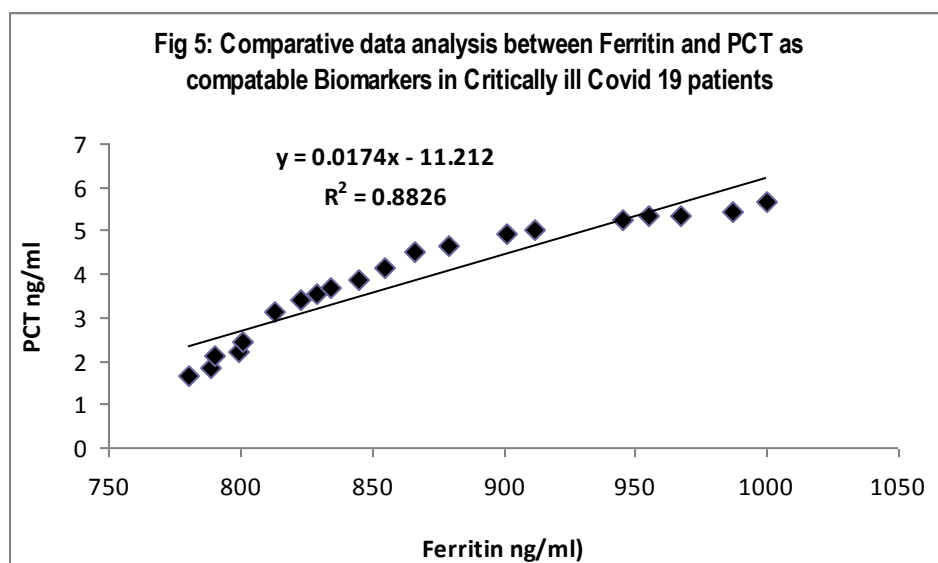
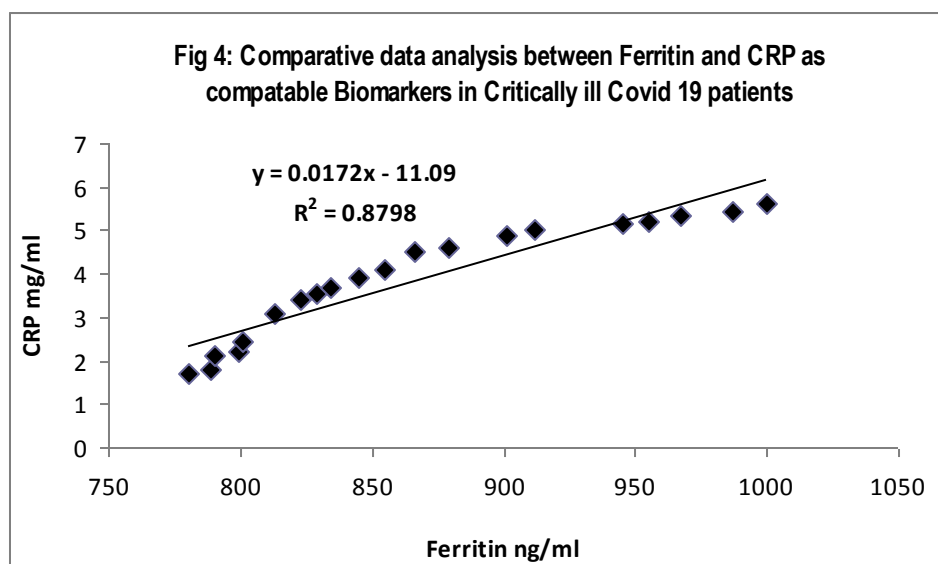
Confirmed, admitted cases of SARS-Covid 19 virus, either in ICUs, HDUs or isolation wards (total 20; 13 males, 07 females) were included in the study. Before inclusion, it was confirmed by assessing and checking Lab information system (LRS) and files that all these patients have data available and been tested for all six inflammatory biomarkers viz D-Dimer, Pro-calcitonin (PCT), Ferritin, Interleukin-6 (IL-6), C-reactive protein (CRP), and Lactate dehydrogenase (LDH). All samples for processing and for analyzing mentioned biomarkers were managed as per protocols described recently [7,9]. Normal reference ranges are D-Dimer < 0.5 μ g/ml, Pro-calcitonin (PCT) < 0.5 ng/ml, Ferritin Males 30-400 ng/ml, Females 15-150 ng/ml, Interleukin-6 (IL-6) < 7.0 pg/ml, C-reactive protein (CRP) < 0.5 mg/ml, and Lactate dehydrogenase (LDH) Males < 225 IU/L, Females < 214 IU/L. Regression correlation analysis was performed using SPSS ver 20.0 (USA) and graphs presented by Y intercept and R², as Ferritin vs IL-6, D-Dimer, LDH, CRP and PCT.

3. Results

Blood samples were collected from patients who were confirmed cases of SARS-Covid 19 infections and admitted either in ICU, HDU or isolation wards. Regression and correlation analysis of Ferritin vs IL6, D-Dimer, LDH, CRP and PCT exhibited very good linear correlation from R² 0.87 to R² 0.95 depicting association of compatibility and inflammatory excitability connection of 87% to 95% (Fig 1 to Fig 5). Regression R² and Y intercept showed Ferritin vs IL-6 as $y = 0.1399x - 90.179$ with R² 0.9507 (Fig 1), vs D-Dimer $Y = 0.0173x - 11.203$, R² 0.8743 (Fig 2); vs LDH $Y = 1.328x - 671.61$ R² 0.8955 (Fig 3); vs CRP $Y = 0.017x - 11.09$ R² 0.8798 (Fig 4); PCT $Y = 0.0174x - 11.212$ R² 0.8826 (Fig 5) exhibiting linear correlation of 95.07%, 87.43%, 89.55%, 87.98% and 88.26%, respectively.







4. Discussion

Presented study described linear regression correlation of Ferritin, an inflammatory biomarker and iron storage protein, versus several other markers viz IL-6, CRP, D-Dimer, PCT and LDH in patients with SARS-Covid 19 infections. Marked correlation exhibited, when ferritin was compared with results of other biomarkers, depicting linear accelerating association amongst all inflammatory components and strongly advocating its high credibility and suggestive usage for not only diagnosis of progression of disease, but also for treatment and evaluating prognosis. Previous and recent past studies reported elevation of these inflammatory biomarkers after SARS-Covid 19 infections, more intensely in critical patients than moderate/non critical and tends to decline during and after recovering [7-11]. Cytokine storms were recognized as one of the reasons for such markedly elevated levels of inflammatory biomarkers [7-9,11]. A recently concluded study reported elevated levels of both Ferritin and IL-6 in patients with Covid 19 infections and receiving Tocilizumab as treatment [1]. Another study strongly suggested continual monitoring of biomarkers especially in critically ill patients of Covid 19 infections [5] for treatment and

prognosis. Prediction of severity of Covid-19 infection via assessing ferritin, IL-6, CRP, D-Dimer, PCT, cardiac Troponins, renal biomarkers and LDH has also been suggested as an important milestone for better treatment and management of such patients [14]. Moreover, D-Dimer and CRP was reported to be an independent factor to predict marked pneumonitis and severity of infections, respectively [12,15]. Studies also showed significantly elevating levels of CRP, Ferritin, IL-6, PCT, D-Dimer in covid-19 patients that ultimately manifest more severe clinical symptoms and thus correlated with poor prognosis [5,16].

5. Conclusion

Current study described comparative correlation and regression analysis of Ferritin in relation to D-Dimer, CRP, PCT and IL-6 and LDH in critically ill covid-19 patients. Regression and correlation data exhibited very good linear correlation from R² 0.87 to R² 0.95 depicting association of compatibility between 87% to 95%, and suggestive high level of credibility of its direct correlation with progression of disease and linear association.

References

- [1]. Farid E, Sridharan K, Alegeai OA, Khawaja SA, Mansoor EJ, Teraifi NA, Qahtani MA, Salman JA (2021). Utility of inflammatory biomarkers in patients with COVID-19 infections: Bahrain experience. 10.2217/bmm-2020-0422 C-2021.
- [2]. Worldometer. COVID-19 coronavirus pandemic updated October 9th, 2021. <https://www.worldometers.info/coronavirus/>
- [3]. Wang Z, Yang B, Li Q, Wen L, Zhang R. (2020) Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin. Infect. Dis.* 71, 769–777
- [4]. Chen G, Wu D, Guo W *et al.* (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Invest.* 130, 2620–2629.
- [5]. Khalid A, Jaffar MA, Khan T, Lail RA, Ali S, Aktas G, Waris A, Javaid A, Ijaz N, Muhammad N (2021) Hematological and biochemical parameters as diagnostic and prognostic markers in SARS-COV-2 infected patients of Pakistan: a retrospective comparative analysis, *Hematology*, 26:1, 529-542, DOI:10.1080/16078454.2021.1950898
- [6]. Zheng Y, Xu H, Yang M *et al.* Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. *J. Clin. Virol.* 127, 104366 (2020).
- [7]. Sultana I, Alam JM, Sardar A, Mahmood SK, Amin M, Ashgar SS, Mahmood ST (2021) Ferritin as Pro-inflammatory marker: Comparative data for Covid-19 and Non-Covid-19, critically ill patients *Chemistry Research Journal*, 6(2):119-124
- [8]. Alam JM, Asghar SS, Ali H, Mahmood SR, Ansari MA. (2021) Profiling of inflammatory biomarkers in mild to critically ill severe acute respiratory syndrome corona virus-19 (SARS Covid-19) patients from Karachi, Pakistan *J Pharm Sci.* doi.org/10.36721/PJPS.2021.34.1.SP.429-433.1 *Pakistan Journal of Pharmaceutical Sciences* ; 34(1):429-433, 2021
- [9]. Alam JM, Baig JA, Mateenuddin S, Ansari MA (2015). Comparative Study on Analytical precision of Iron Profile on conventional Hitachi 912 and modular cobas 6000 c501 systems. *International Journal of Chemical and Pharmaceutical Sciences.* Vol. 06 (1), PP- 1-5.
- [10]. Banchini F, Cattaneo GM, Capelli P (2021) Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non-COVID-19 patients. *World Journal of Emergency Surgery*, 16:9 <https://doi.org/10.1186/s13017-021-00354-3>.
- [11]. Onur ST, Altın S, Sokucu NM, Fikri BJ, Barça T, Bolat E, Toptaş M (2021) Could ferritin level be an indicator of COVID-19 disease mortality? *J Med Virol.* 93:1672–1677.



- [12]. Velavan TP, Meyer CG. (2020). Mild versus severe COVID-19: Laboratory markers. *International Journal of Infectious Diseases*, 95: 304–307.
- [13]. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. (2020). Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*; 191(July):148–50.
- [14]. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. (2020) The role of biomarkers in diagnosis of COVID-19 - a systematic review. *Life Sci.* 254, 117788.
- [15]. Tan C, Huang Y, Shi F *et al* (2020). C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J. Med. Virol.* 92, 856–862 (2020).
- [16]. Huang I, Pranata R, Lim MA, et al. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis.* 2020; 14: 1753466620937175.