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Ferritin as Pro-inflammatory marker: Comparative data for Covid-19 and Non-Covid-19, critically ill patients

Ishrat Sultana[1], Junaid Mahmood Alam[1], Afsheen Sardar[1], Sheikh Khalid Mahmood[1], Mahwish Amin[1], Sarah Sughar Ashgar[2], Syed Riaz Mahmood[3]

[1]Department of Clinical Biochemistry lab services and Chemical Pathology, Liaquat National Hospital and Medical College, Karachi-74800. Pakistan
[2]Department of Anatomy, Sir Syed College of Medical Sciences for Girls
[3]Department of Pathology, Lyari General Hospital, Karachi
Corresponding author: dr_jmalam@hotmail.com

Abstract *Background*: Out of many untoward responses, inflammatory response to Covid 19 infections is known to be very potent and multi-dimensional. Several articles and studies based on Ferritin as a pro-inflammatory marker, suggested its diagnostic efficacy in SARS-Covid 19 infections and already known critical conditions. *Aim:* Present study described a comparative data regarding levels of Ferritin in SARS Covid 19, critically ill patients versus critically ill patients with hematological disorders, devoid of Covid 19 infections. *Materials and Methods*: A total of 48 patients, divided into Covid 19 (n = 28, Males = 20 female 08) and non-Covid-19 critically ill patients (n = 20, Male = 15, F = 05) were included in this study. SARS Covid-19 positive patients were all critically ill thus selected accordingly. Ferritin, ProCalcitonin (PCT), C-Reactive Protein (CRP), coagulation marker-D-Dimer, chemical analytes, Protein, Albumin, BUN, Bilirubin, Creatinine, and enzymes, Lactate Dehydrogenase (LDH), γ-Glutamyl transpeptidases (gGT), Alkaline phosphatase (ALP) were routine analyzed by internationally recognized standard methods described earlier for all patients. *Results*: Except, total biliribin (< 0.01), γGT (P<0.042) and CRP (P<0.045), none of the parameters exhibited any significant variation or difference in both categories of patients when compared using Student's t-test. *Conclusion*: Ferritin, been a storage protein, elevated due to possible adverse effects on signaling pathways, consequentially causing alterations in patho-physiology, in cases of whether patients has Covid-19, got critically ill or became critically ill due to other clinical conditions/diseases.

Keywords Ferritin, Pro-inflammatory marker, Covid-19, Non-Covid-19

1. Introduction

Severe Acute Respiratory Syndrome Covid 19 (SARS-Covid 19) spread like hay-fire since January 2020 and as of today, world wide total infected cases are 123 million, deaths 2.71 million and recovery 69.8 million (WHO, 2021, accessed 21st March). In Pakistan total recorded cases is 627K, deaths 13,843 and recovery 582K (WHO, accessed 21st March 2021). As reported in several hundred articles, reports and documents, multi system dysfunction, alterations, disparity is normal physiology are the basis of Pathogenesis of Covid 19 disease [1-6]. Out of many untoward responses, inflammatory response to Covid 19 infections are known to be very potent and multi-dimensional [2-5]. Several important pro-inflammatory markers had been identified, tested and reported as

indicators of Covid 19 disease intensity, progression and a possible positive or negative prognosis [7-9]. C-reactive protein, D-Dimer, Procalcitonin, Interleukins, Ferritin, and enzymes such as lactate dehydrogenase, phosphatases and/or transpeptidases, were reported as prime markers for the diagnosis and prognosis of Covid-19 infections [10-15]. Been the central player in iron metabolism, the iron storage protein, Ferritin, reported to be a significant pointer for not only assessing iron status, but also indicates any abnormality in on going Iron metabolism [16-18]. Several articles and studies based on Ferritin as a pro-inflammatory marker, suggested its diagnostic efficacy in SARS-Covid 19 infections and already known critical conditions, whether manifested as severe pneumonia, haemophagocytic lymphohistiocytosis, Lymphopenia or bleeding/coagulation disorders [1, 7, 8, 12, 19-21]. Therefore, Present study described a comparative data regarding levels of Ferritin in SARS Covid 19, critically ill patients versus critically ill patients with hematological disorders, devoid of Covid 19 infections.

2. Materials and Methods

2.1 Patients selection and research design

A total of 48 patients, divided into Covid 19 (n = 28, Males = 20 female 08) and non-Covid-19 critically ill patients (n = 20, Male = 15, F = 05) were included in this study. SARS Covid-19 positive patients were all critically ill thus selected accordingly (Liu et al., 2020). Critically ill patients admitted with symptoms and signs of oxygen saturation ≤ 85%, heart rate 110 beats/minute and essentially requiring ICU admission and ventilation assistance. Furthermore, diabetes, hypertension, cardic-dysfunction and renal insufficiency were some of the underlying condition noted in Covid -19 patients. Non Covid-19 but critically ill patients were total of twenty, with end stages of untreated hemochromatosis (n =2), Hodgkin's' lymphoma (n = 2), Trauma injuries (n = 3), Hepatitis C cirrhosis, complications (n = 7), cardiomyopathy (n = 4) and Pulmonary infiltration (suspected TB, n = 2) with underlying co-morbid such as diabetes, hypertension, pulmonary dysfunction, cardic-dysfunction, renal insufficiency, neurological problems. Study was completed at Chemical Pathology and Clinical Biochemistry lab services, Liaquat National Hospital and Lyari General Hospital, Karachi.

2.2 Determination of Ferritin, inflammatory biomarkers, chemical analytes and Enzymes

Routine chemistries and other diagnostic tests were performed routinely, data gathered and logged. Routine chemistry and hematology was performed by standardized methods (Tietz, 1995). Ferritin, ProCalcitonin (PCT), C-Reactive Protein (CRP), coagulation marker-D-Dimer, chemical analytes, Protein, Albumin, BUN, Bilirubin, Creatinine, and enzymes, Lactate Dehydrogenase (LDH), γ-Glutamyl transpeptidases (gGT), Alkaline phosphatase (ALP) were routine analyzed by internationally recognized standard methods described earlier [22-29].

2.3 Statistical Analysis

Both Patients' groups were compared with each other as critically ill Covid-19 and non-covid 19. Data considered significant using students t-test, when P considered as $P< 0.05$. All other data were either presented as percentage or mean ±SD.

3. Results

A total of 48 patients were selected for this study, Covid 19 (n = 28, Males = 20 female 08) and non-Covid-19 critically ill patients (n = 20, Male = 15, F = 05). Critically ill patients (n = 28) admitted with symptoms and signs of low oxygen saturation and essentially requiring ICU admission and ventilators. Diabetes, hypertension, cardic-dysfunction and renal insufficiency were some of the underlying condition noted in Covid -19 patients. Non Covid-19 but critically ill patients were total of twenty, with several end stages medical conditions and diseases, with underlying co-morbid such as diabetes, hypertension, pulmonary dysfunction, cardic-dysfunction, renal insufficiency, neurological problems. Age (yrs) was 54.35 ±15.40 and 50.15 ±16.30 respectively for Covid-19 and non covid-19 patients whereas percentage distribution of males and females were 20 (71.42%) and 08 (28.57%); and

15 (75.00%) and 05 (25.00%), respectively. Patients in both categories were with co-morbid with renal insufficiency in common numbers and rest of the clinical conditions was variable as per presentation (table 1).

Routine chemistries and other diagnostic tests were performed routinely as per physician's advice, data gathered and logged. Urea, Creatininr, etc and Ferritin, ProCalcitonin (PCT), C-Reactive Protein (CRP), coagulation marker-D-Dimer, chemical analytes, Protein, Albumin, BUN, Bilirubin, Creatinine, and enzymes, Lactate Dehydrogenase (LDH), γ-Glutamyl transpeptidases (γGT), Alkaline phosphatase (ALP) were tested as per clinical requirements. Except, total biliribin (< 0.01), γGT (P<0.042) and CRP (P<0.045), none of the parameters exhibited any significant variation or difference in both categories of patients when compared using Student's t-test with P<0.05 (table 2).

Table 1: Demography and description of co-morbid in both Covid-19 positive and non-covid-19 critically ill patients

Parameters	**Covid-19 patients (n = 28)**	**Non-covid-19 patients (n = 20)**
Age (yrs)	54.35 ±15.40	50.15 ±16.30
Gender		
Males	20 (71.42%)	15 (75.00%)
Females	08 (28.57%)	05 (25.00%)
Co-morbid		
Diabetes	7	6
Hypertension	12	5
Cardiac-myopathy	5	3
Renal insufficiency	4	4
Neurosis	3	4
Pulmonary dysfunction	7	5

Table 2: Characteristic pattern of Ferritin, chemistries and biomarkers in SARS-COVID-19 and Non-Covid 19 critically ill patients

	Covid-19	**Non-Covid 19**
Blood biochemistry markers		
Total protein (6.3-7.9g/dl)	6.35± 3.35	6.10± 2.85
Albumin (3.0-5.0 g/dl)	3.00± 1.75	3.2± 2.60
Total bilirubin (< 1.2 mg/dl)	8.85± 3.05	5.55± 7.00**A
γ-Glutamyl transpeptidase (< 60 U/L)	93.10± 20.60	88.20± 30.15*B
Alkaline phosphatase (30-130 U/L)	95.55± 24.15	91.25± 33.30
Lactate dehydrogenase (135-225 U/L)	575.45 ± 101.65	561.40± 147.80
Blood urea nitrogen (7-20 mg/dl)	35.20± 5.90	33.15± 8.65
Serum creatinine (0.84-1.21 mg/dl)	2.95± 0.95	2.45± 1.10
Coagulation function marker		
D-dimer (< 0.5 µg/mL)	7.95± 2.35	7.82± 3.05
Infection/Inflammatory biomarkers		
Procalcitonin (< 0.5 ng/mL)	1.21± 0.16	1.05± 0.40
C-reactive protein (< 0.5 mg/L)	13.95± 1.10	10.30± 2.65*C
Serum ferritin (15-400 ng/mL)	1421.4±120.15	1452± 121.60

Where P< 0.05; ** significant A= < 0.01; * mildly significant B = < 0.042, C = < 0.045

4. Discussion

What we have learned from last year's Covid-19 pandemic that it's a multi-layered, multi-dimensional and multi-facade consequential, severely reactionary, and full of untoward effects and morbid outcome's syndrome, able to create marked inflammatory responses, which most of the time uncontrollable and deadly. To check intensity of pro-inflammatory reactions or responses, scientists, clinicians, epidemiologist and infectious disease experts suggested determination of pro-inflammatory markers such as C-reactive protein, D-Dimer, Procalcitonin, Interleukins, Ferritin, and enzymes such as lactate dehydrogenase, to diagnose and for proper prognosis of Covid-19 infections. More recently in later part of 2020, ferritin emerged as one of the biomarkers that clearly provide suitable information for categorizing Covid 19 patient's according to severity of infections [1,2,30,31]. Malaise, coughing, high fever, myalgia and goes to developing acute respiratory distress syndrome (ARDS), with underlying lymphopenia, coagulation disorders, haemophagocytic lymphohistiocytosis and mild to severe pneumonia were noted as co-morbid and in each and every clinical state, there was a decline in circulating iron and elevation in Ferritin, thus manifesting consequence disease severity and cytokine storm [7-9, 11, 19, 20-21].

In our study presented here, we have found no difference in the higher levels of ferritin in Covid-19 ICU admitted and non-covid 19 critically ill patients, neither noted any difference between altered levels of other inflammatory biomarkers expect total bilirubin, gGT and CRP in both groups of patients. This suggest a notion that Ferritin, been a storage protein, and tightly regulated via several genetic steps, gets elevated, citing adverse effects on signaling pathways due to critical patho-physiology, in cases of whether patients has Covid-19 and then got critically ill or became critically ill due to other clinical conditions/diseases [9, 16, 32]. It was reported that cytokine does regulate post-transcription of ferritin synthesis, can alter ferritin concentration via nitric oxide and/or can induce over stimulation of hepatocyte secretions [33-35]. Moreover, earlier studies also pointed out that high ferritin levels not only depicts iron overload, but also systemic inflammation, autoimmunity, infectious or malignant conditions [9]. Some of the condition that manifest very high ferritin leves are macrophage activation syndrome (MAS), adult-onset still disease (AOSD), catastrophic anti-phospholipid syndrome (cAPS) and sepsis; conditions that were identified as 'hyperferritinemic syndrome' [36]. Both MAS and haemophagocytic lymphohistiocytosis (HLH) can trigger mass cytokine release, known as cytokine storm, corollary of marked systemic infection such as Covid 19 SARS. In present study, similar pathway might have been instigated which leads to elevated ferritin levels, in critical categories, Covid-19 and non-Covid 19.

5. Conclusion

In present study we have described comparative data regarding elevated levels of Ferritin in SARS Covid 19, critically ill patients versus Non-cobid 19 critically ill patients with hematological and other disorders. We noted no difference in the higher levels of ferritin in Covid-19 ICU admitted and non-covid 19 critically ill patients, neither noted any difference between altered levels of other inflammatory biomarkers expect total bilirubin, gGT and CRP in both groups of patients. Thus Ferritin, been a storage protein, and tightly regulated via several genetic steps, gets elevated, due to probable adverse effects on signaling pathways, consequential outcome of critically altered patho-physiology, in cases of whether patients has Covid-19, got critically ill or became critically ill due to other clinical conditions/diseases.

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