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# Association of Serum Lactate Dehydrogenase and Ferritin with the Severity of Infection Caused By Severe Acute Respiratory Syndrome Corona Virus 2 (Sars Cov-2).

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**ABSTRACT:**

Twenty crore of patients effected globally with around forty three lakhs death till now in this pandemic caused by corona virus disease 19 (COVID-19). India also is one of the badly affected countries with 3.2 crore cases with 4.2 lakhs death.

Serum LDH and ferritin are among most studied parameters in COVID-19 disease. Though many studies on these two parameters in COVID were done in different part of the world (with comparatively less study on ferritin); in India, studies in this aspect are comparatively less. In this present study the association of serum LDH and ferritin with the severity of the disease was tried to find out to verify the results of other similar studies and the correlation of both in severe and non -severe patients also tried to find out.

**Materials and methods:**

Out of 100 RT PCR positive COVID patients, 50 from ward and 50 others from ICU were included in the study as per the inclusion-exclusion criteria also named as non-severe and severe group. Then their on- admission serum LDH and ferritin level was obtained from laboratory information system (LIS) and patient data also was obtained from hospital data base. Then the data was analyzed statistically.

**Result:**

The difference in the mean value of LDH between ward and ICU patients (306.75±140.37 and 487.63±223.28 respectively) was statistically significant ($p<0.0001$). Similarly, the difference in serum ferritin between these two groups (210.23±218.32 and463.37±295.86 respectively) is also statistically significant (<0.0001). There was a statistically significant moderate positive correlation ( $R = 0.6938$ and $p<0.00001$) between serum LDH and ferritin in ward, but this correlation in ICU was insignificant and very weakly positive($R = 0.0605$ and $p = 0.5498$).

**Conclusion:**

Both serum LDH and ferritin in COVID patients are associated with disease severity which also can be used as a useful marker to identify potentially high risk patients and also for monitoring purpose. But serum LDH and ferritin raises proportionately in mild to moderate COVID but in severe form they raise out of the proportion without any correlation in between them.

**KEYWORDS:** COVID-19, ferritin, lactate dehydrogenase (LDH),

## I. INTRODUCTION:

It has been now approximately two years; the universe is facing the worst pandemic ever caused by Severe Acute Respiratory Syndrome Corona Virus 2 or SARS- COV-2 virus as named by WHO. The disease was also named corona virus disease 2019 or COVID-19 [1].

This deadly virus was initially signature its typical symptoms in Wuhan, China [2]. Symptoms started with fever, cough, myalgia which mimic a viral respiratory tract infection but often turned into atypical pneumonia and lastly death in severe cases especially in immune-compromised host.

Gradually the virus expanded its claws and grasped almost entire world with forty three lakhs death and around twenty crore of patient burdens globally is sufficient enough to call this pandemic as the deadliest pandemic ever [3].

Viral threat to the human civilization is not a new thing. Earlier severe acute respiratory syndrome (SARS, in 2002 at China), Middle East

respiratory syndrome (MERS in 2012 at Middle East countries) etc. also were appeared as a threat to human life, some of them even were more lethal than the COVID-19 disease but unlike COVID, they were localized in particular regions unlike SARS-COV-2 [4,5]

Diagnostic laboratories are playing an important role in this pandemic, starting from detection of SARS COV2 virus through RT PCR to find out various markers of COVID-19 disease to pick up patients who are in potentially high risk of developing the severe form of the disease. Earlier many parameters were studied as a marker of this disease based on experiences of other viral endemics but with time some of the parameters proved their efficacy to identify potentially high risk patients at an early stage of the disease. These parameters are serum lactate dehydrogenase (LDH), serum ferritin, C reactive protein (CRP), serum IL-6 level, lymphocyte count etc.[6,7] In the initial phase of the pandemic multiple small studies in this regard were published which are mostly from China but with the advancement of time now many original research works, meta-analysis etc. with larger population size have published from different corner of the world which showed the efficacy of these markers in COVID.

India is also not spared by this pandemic with burden of 3.2 crore cases with 4.2 lakhs casualty which made it one of the worst effected countries [8]

Lactate dehydrogenase (LDH) is an enzyme required for the subcellular level conversion of pyruvate to lactate. It is found in different organ system in human body in the form of its five isoenzymes (LDH-1 to LDH-5). Each of them has their own predominance in particular organ system [9].

SARS COV2 virus enters in human host via respiratory track, more preciously through lung. Most acceptable theory regarding its entry says the viral spike protein binds with the angiotensin converting enzyme II (ACEII) which is found abundantly in alveolar cells of lung. This complex binding facilitates the entry of virus in human host [10]. That is why respiratory symptoms are common in all COVID patients which in turn develop into atypical pneumonia in severe disease especially in immune-compromised hosts.

So initial LDH rise may be due to rise in LDH-3 isoenzyme, which is predominant in lung; secondary to lung tissue injury by infection or atypical pneumonia. But as the disease progresses towards its severe form, further rise in serum LDH level occurs in conjunction to the previous one secondary to involvement of other organs where other isoenzymes of LDH were predominant, like liver, kidney, and myocardium by cytokine storm [9].

Ferritin mostly is a cytosolic protein with twenty four subunits. It is known for intracellular iron storage and iron homeostasis. Though the sources and pathways of ferritin secretion are unclear till date, but it has been found that macrophages, hepatocytes and kufper cells can secret ferritin. Each subunit of ferritin is made of two types of protein named as H protein and L protein. Studies showed that inflammation stimulates expression of H subunit and H-ferritin is capable of exhibiting pro-inflammatory and immune-suppressive action [11]. Severe inflammatory conditions such as in COVID where uncontrolled release of pro-inflammatory cytokines (also known as cytokine storm) which causes hyper-ferritinemia. This may be due tosecretion of ferritin from macrophages which also are involved in production of immune cells in lung parenchyma. So, active ferritin production mainly depends on the number of macrophages present. Apart from this some pro-inflammatory cytokines like interleukin-6 (IL-6) induces ferritin production in hyper-inflammatory states like COVID. Evidences suggest that there might be some complex feedback mechanisms working between pro-inflammatory cytokines and ferritin. Ferritin may act as a mediator of immune system by working as a signaling molecule [12].

Many studies worldwide have published regarding the involvement of LDH and serum ferritin in COVID-19 disease (with comparatively less studies on serum ferritin). But in India comparatively less number of studies was done in this regard. In this present study the association of serum ferritin and LDH with the severity of COVID-19 disease is tried to find out to verify the result of the other similar studies done in different part of the world and most importantly, correlation of serum ferritin and LDH with the disease severity also statistically sorted out so that this can be used for assessment of the COVID patients in early stage of the disease.

## II. MATERIALS AND METHODS:

This retrospective observational study was conducted in the Department of Biochemistry, Silchar Medical College and Hospital, Cachar, Assam. Sample size was calculated using online sample size calculator considering 95% confidence level and 5% margin of errors and population size 130 (average admitted patients in study period). Total one hundred RT PCR positive COVID patients were enrolled for the study who fulfilled the

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inclusion-exclusion criteria mentioned below. Out of them fifty patients were enrolled from COVID ward and remaining fifty from COVID ICU. Enrolled patients from COVID ward were considered as non-severe group and patients from COVID ICU were considered as severe group. Now all the required laboratory data (serum LDH and serum ferritin level on admission) was obtained from Laboratory Information System (LIS) of central composite laboratory. Patient's data was obtained from hospital database.

**Inclusion criteria:**

- Patients with age more than 18 years.
- Patients diagnosed with COVID-19 infection by RT-PCR method and admitted in either the ward or the ICU.

**Exclusion criteria:**

- Patients diagnosed with hematological malignancies or solid tumors.
- Patients taking immunosuppressive drugs for another disease.
- Patients with a recent history of solid organ transplant or bone marrow transplant.
- Patients with any hematological disorder like anemia of any type,

Hemochromatosis, etc.

- Patients with chronic inflammatory conditions like rheumatoid arthritis etc.

**Statistical analysis:**

The obtained data was analyzed statistically using Microsoft excel, Graph pad. Continuous variables were represented as mean ± standard deviation (SD) and categorical variables were represented as percentage. For the association of serum ferritin and LDH with the severity of the disease, unpaired t test was done and to find out the correlation between ferritin and LDH, Pearson correlation coefficient was calculated. Details of the statistical analysis are discussed in result section.

**Design of the study:**

It is a retrospective observational study.

**Duration of the study:**

The duration of the study was for six months, from November 2020 to May 2021.

**ETHICAL CONSIDERATION:**

The study was done by abiding all the ethical norms of the Institute.

## III. RESULT:

Data of total one hundred COVID patients (fifty from ward and fifty from ICU) was analyzed.

Data regarding the age of the study participants in COVID ward shows, mean age was 46.42 years with standard deviation 14.96 years. Age group wise distribution shows maximum patients here belonged to the age group of 40yrs to 59 years (around 42%) followed by 34% belonged to age group 20yrs to 39 years. 24% patients belonged to the age group of 60 years to 79 years. Details of age distributions in COVID ward are given in table no 1.

**Table no 1**: **Distribution of the study participants in ward according to age (n=50)**

| Age groups ( in year) | Frequency | Percentage |
|---|---|---|
| 20 – 39 | 17 | 34 |
| 40 – 59 | 21 | 42 |
| 60 – 79 | 12 | 24 |
| 80 and above | 00 | 00 |

Mean age of the patients of ICU was 62.9 years with standard deviation (SD) 12.55 years. Here maximum patients fell into comparatively older age group (58% patients belonged to age group 60yrs to 79 years.). 32% patients were in age group of 40 years to 59 years, 6% patients were in age group of more than 80 years and 4% in younger age group of 20 years to 39 years. Details are described in table no: 2.

**Table no 2**: **Distribution of the study participants in ICU according to age (n=50)**

| Age groups ( in years) | Frequency | Percentage |
|---|---|---|
| 20 – 39 | 02 | 04 |
| 40 – 59 | 16 | 32 |
| 60 – 79 | 29 | 58 |
| 80 and above | 03 | 06 |

Gender wise distribution shows in COVID ward 60% were male patients whereas in COVID ICU male patients were dominant with 64%. Details of gender analysis is described in table no 3.

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**Table 3: Details of gender analysis**

| | COVID ICU participant (n=50) | COVID ICU participant (n=50) | COVID Ward participant (n=50) | COVID Ward participant (n=50) |
|---|---|---|---|---|
| Gender | Frequency | percentage | frequency | percentage |
| Female | 18 | 36 | 20 | 40 |
| Male | 32 | 64 | 30 | 60 |

Religion wise distribution shows in ward 90% of the patients belonged to Hindu community and 10% were from Muslim community and in ICU 90% were from Hindu community 8% were from Muslim community and only 2% belonged to other community.

When analyzing the serum LDH data, it has been found that COVID ward patients had mean serum LDH of 306.75 with standard deviation 140.37 while COVID ICU patients had mean serum LDH 487.638 with standard deviation of 223.28 and the difference was statistically very significant with p value of <0.0001 while p<0.05 taken as significant. Details is described in table no 4.

**Table 4: Comparison of serum LDH between ICU and ward patients**

| Blood parameters | Mean (SD) | | p value* |
|---|---|---|---|
| | ICU (n=50) | WARD (n = 50) | |
| LDH | 487.63(223.28) | 306.75(140.37) | <0.0001 |

*****Done by unpaired t test with confidence interval of 95%

When analyzing the data of serum ferritin, it has been seen that mean serum ferritin in COVID ward patients was 210.23 with standard deviation 218.32. But in COVID ICU patients mean was 463.3748 with standard deviation 295.86 and the difference too was statistically very significant with p value of <0.0001 (p<0.05 was taken as significant). Details is described in table no 5.

**Table 5: Comparison of serum Ferritin between ICU and ward patients**

| Blood parameters | Mean (SD) | | p value* |
|---|---|---|---|
| | ICU (n=50) | WARD (n = 50) | |
| FERRITIN | 463.37(295.86) | 210.23(218.32) | <0.0001 |

*****Done by unpaired t test with confidence interval of 95%

While analyzing the correlation between LDH and ferritin among COVID ward patients by Pearson correlation coefficient (R), it has been seen that R value was 0.6938. This was a moderate positive correlation which indicates high value of LDH was correlated with high value of ferritin and p value was <0.00001 while p<0.05 taken as significant. This suggests the correlation was statistically significant. Details are described in table no 6 and figure no 1

**Table-6: Showing the correlation between LDH and Ferritin in Ward**

| | **LDH** | **FERRITIN** |
|---|---|---|
| LDH | | 0.6938 |
| Pearson correlation | | |
| P value | | <0.00001 |

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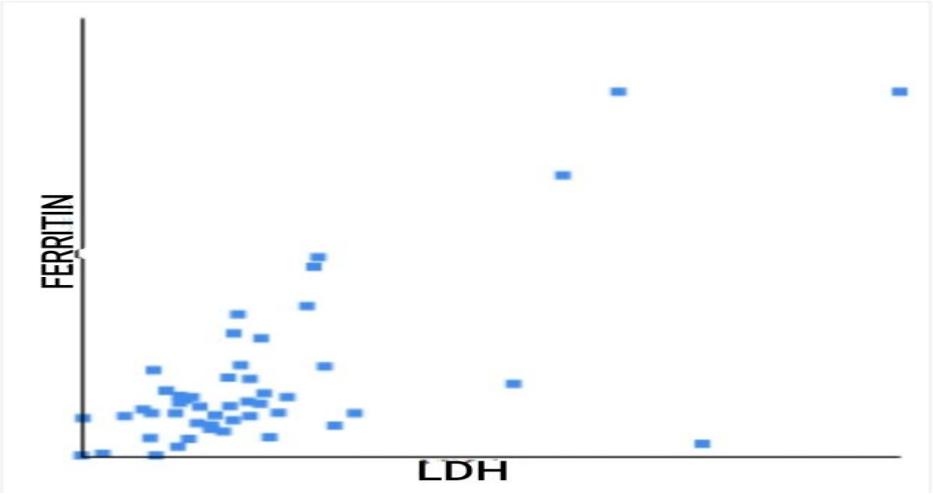
| | | |
|---|---|---|
| FERRITIN<br>Pearson correlation<br>p value | 0.6938<br><0.00001 | |

**Figure no 1: Plot diagram of correlation between LDH and ferritin among ward patients**




Pearson correlation coefficient (R) of serum LDH and ferritin in COVID ICU patients was 0.0605 which indicates a very weak positive correlation between these two. While calculating the p value, it was 0.5498 ($p<0.05$ taken as significant). So statistically this correlation was not significant. Details in table no 7 and figure no 2.

**Table-7: Showing the correlation between LDH and Ferritin ICU**

| | **LDH** | **FERRITIN** |
|---|---|---|
| LDH<br>Pearson correlation<br>P value | | 0.0605<br>0.5498 |
| FERRITIN<br>Pearson correlation<br>p value | 0.0605<br>0.5498 | |

**Figure no 2: Plot diagram of correlation between LDH and ferritin among ICU patients.**

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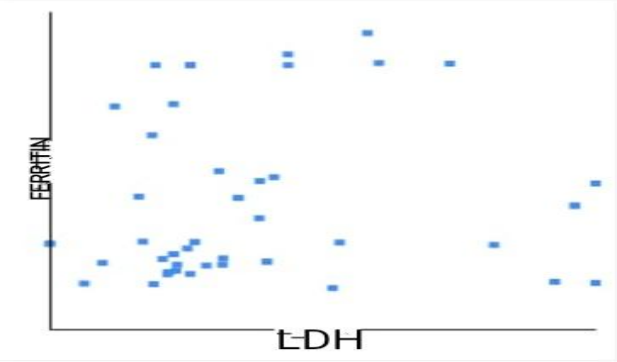


## IV. DISCUSSION:

A good number of studies were published with the pace of time regarding the serum LDH and ferritin as a marker of COVID-19(in comparison less study on serum ferritin) but in India number of studies in this aspect is comparatively less. Here discussion of the present study result is done in comparison to the findings of the similar studies conducted in recent time.

**Wu et al.** in their study named "Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia" with 87 diagnosed COVID patients (77 non severe and 10 severe patients) found 47 of them were male and 40 others were female and their median age were 44 years, 35.6% belonged to the age group of more than 50 [13].

**Najim R H et al.** in their case control study "Biochemical and hematological parameters as a predictor for COVID -19 infections in 65 patients diagnosed by real time –PCR in Kirkuk city" found the mean age of their RT PCR positive study participants (total 130 study participants, 65RT PCR positive and 65 RT PCR negative as control) was 44.2 years with SD 13.1years. 67.7% of their study participants were male [2].

**Zhang ZL et al.** in their review article named "Laboratory findings of COVID-19: a systemic review and meta- analysis" with 28 articles covering 4663 patients, found mean age of the patients was 48.4 years and 46.7% were female patients [14].

In the present study mean age of COVID ward patients were 46.42 years with standard deviation 14.96 years and of COVID ICU patients were 62.9 years with standard deviation (SD) 12.55 years. Around 42% patients were in the age group of 40yrs to 59 years in ward while 58% patients belonged to age group 60yrs to 79 years in ICU. In COVID ward there was male dominancy with 60% while in COVID ICU there was majority of male too with 64%. The pattern of gender and age distribution of the present study is almost similar to other same kind of studies.

**Zhang ZL et al.** in their meta-analysis observed that raised serum LDH level (in 46.2% patients) was one of the most consistent laboratory findings in enrolled COVID patients. They further sorted out seven studies where participants were divided into severe and non-severe groups covering 1905 patients in total. They found that increased serum LDH level had the significant high risk of developing severe form of the disease while comparing with the non- severe group (percentage wise 41.7% and $p<0.001$) [14].

**Mardani R, Vasmehjani AA et al** in their study titled "Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study" found mean LDH level was 465.2 ±100.2 and area under curve was 0.835 in RT PCR positive COVID group of patients (total 200 patients were participated in that study and among them 70 were RT PCR positive). They also observed serum LDH was significantly high in RT PCR positive patients ($p<0.0001$) [15].

**Henry BM et al** did a meta-analysis named "Lactate dehydrogenase levels predict coronavirus disease 2019(COVID-19) severity and mortality: A pooled analysis" covering 1532 COVID patients. Out of them serum LDH was compared between severe and non-severe group in seven studies comprising 1206 patients. They found total 49.8% patients presented with raised LDH level. While comparing it between severe and non-severe groups, they observed 84.6% patients in severe group had raised LDH level compare to 43.3% in non –severe group [16]. They got raised serum LDH value was associated with increase odds of severe COVID-19 outcome in maximum studies.

**Wu et al.** in their study found that on admission mean LDH of all COVID patients participated was 495.1 ±28.22 U/L. While in non-severe group it was 442 ±17.47 U/L but in severe

group of patients the LDH mean was 1040 ±158.3 U/L and the difference was very significant statistically ($p<0.01$). They also showed that the LDH level was correlated positively with the resolution of pneumonia radio logically with correlation coefficient ($r=0.53$and $p<0.05$) [13].

In maximum of the studies concluded with the decision that serum LDH level is associated with the severity of the disease and can be used as a marker for assessment and monitoring of the patients.

In the present study the mean LDH of non-severe patients that is patients in the COVID ward was 306.75 U/L with SD 140.37 U/L whereas the mean LDH value of severe group of patients or patients admitted in COVID ICU was 487.638 U/L with SD 223.28 U/L. The difference between these two group was very significant statistically with p value of <0.0001.

These findings are very much similar to the other studies of same type, discussed above. So on-admission raised serum LDH level is associated with the disease severity in COVID-19; this fact is verified through these findings of the present study.

**Banchini F et al.**.in their study named "Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non-COVID-19 patients" found serum ferritin as a marker of inflammation in COVID-19 disease when they compare the inflammation (assessed by the conventional assessment for inflammatory process) in non-COVID surgical patients. They found 52% of RT PCR positive COVID patients had higher serum ferritin level with mean of 674ng/ml with interquartile range (IQR) 1248ng/ml and the expired COVID patients had higher median value of 1563ng/ml with IQR 1637 ng/ml. While the median value of serum ferritin was compared between RT PCR positive patients and swab negative patients, it was seen that the difference was very significant statistically ($p<0.0001$).They also conclude that iron metabolism may have direct involvement in COVID-19 infection [17]

**Deng F et al**. in their original research work found that not only serum ferritin in the time of admission was significantly higher in critical group of patients compared with moderate to severe group, but it's level was around three times higher in expired patients with COVID-19 infection than the survivor group. The level of serum ferritin was positively correlated with other pro-inflammatory cytokines also [18].

**Kishan J H et al** in their study named " serum ferritin, serum LDH and D-Dimer in correlation with the outcome in COVID-19" showed that there was no significant difference in outcome when D-Dimer was considered, but there were significant difference in outcome with LDH and serum ferritin with p value of <0.001 and 0.016 respectively. Their study was done on 108 diagnosed COVID patients with considered parameters, serum LDH, ferritin and plasma D-Dimer combined [19].

In the present study the mean of serum ferritin level in non- severe group of patients (patients admitted in COVID ward) was 210.23 ng/ml with standard deviation (SD) of 218.32 ng/ml whereas in severe group ( participants admitted in COVID ICU) the mean ferritin level was 463.37 ng/ml with SD 295.86 ng/ml. The difference of ferritin level between these two groups were extremely significant statistically with a p value of <0.0001.

These findings suggest higher value of serum ferritin on admission can reflect the severity of the disease in COVID.

In the present study in addition to find out the association of serum LDH and ferritin with the severity of COVID-19 disease, the correlation between these two both in severe and non-severe group is tried to find out. In non- severe group it was found that there was a statistically significant moderate positive correlation which indicates high value of LDH was correlated with high value of ferritin, and p value was <0.00001 with Pearson correlation coefficient (R) value of 0.6938. In severe group,there was a clinically insignificantvery weak positive correlation between LDH and ferritin with Pearson correlation coefficient value (R) 0.0605 and p value 0.5498. These findings regarding the correlation of serum LDH and ferritin on admission of COVID patients suggest, in non-severe to moderate cases of COVID, the rise in serum LDH and serum ferritin is related with each other but in severe cases where massive inflammation takes place in the form of cytokine storm, they rise further leaving behind the correlation seen before.

## V. CONCLUSION:

From the discussion above it can be concluded that in COVID-19 disease, elevated level of both the serum LDH and ferritin is associated with the disease severity and can be used as a marker to pick up the potentially high risk patients who may develop the severe form of the disease. These two parameter raises proportionately in mild to moderate COVID but in severe form they raise out of the proportion without any correlation in between them.

**CONFLICT OF INTEREST:**

There is no conflict of interest.

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