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RESEARCH ARTICLE

ASSOCIATION OF INFLAMMATORY MARKERS IN COVID 19 PATIENTS

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Abstract

Objective: we aimed to provide overview of association of inflammatory markers with severity of Covid 19.

Methods: 100 patients admitted in Shri Mahant Indresh Hospital Covid Ward with positive RT PCR. Serum samples taken and run on VITROS 5600 and reported for CRP, FERRITIN, LDH, Procalcitonin, D-dimer & TLC.

Results: with 100 patients 34 were females & rest 66 were males. Out of which all parameters run on all patients. Mean age for males 48.86 ± 15.29 & Mean age for females 43.11 ± 16.21 . In all 6 parameters only 3 parameters CRP, LDH, Ferritin had significance in the study with p value $< .01$. Whereas rest 3 parameters TLC, D-dimer & Procalcitonin had non significant value. D-Dimer had p value 0.483. Procalcitonin p value 0.23. TLC p value 0.08. therefore these parameters in my study was not significant inflammatory markers in patients of Covid 19.

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Introduction:-

COVID-19 Pandemic In India

First case of Covid- 19 infection reported in Kerala India on January 30 2020, a 20 year old female presented that she had returned to Kerala from Wuhan China on January 23rd. India currently has the largest number of confirmed cases in Asia and has the second highest number of confirmed cases in the world after United States with more than 9,000,000 reported cases of COVID-19 infection and more than 100,000 death per day. Cases hit mid September in India with over 90,000 case reported per day and have since come down below 40,000 in December By mid may 2020 hey 60s accounted for around half of all reported cases in the country Mumbai, Delhi, Ahmedabad, Chennai, Pune, Kolkata as of 10 September 2020 lakshadweep is the only region which has not reported a case on 10 June India's recoveries exceeded active cases for the first time infection rate started to drop significantly in September and the number of daily new cases and active cases starts to decline rapidly.

Signs and Symptoms of Covid 19

Covid 19 effects different people in different ways most infected people will develop mild to moderate illness and recover without hospitalization most common symptoms:

Fever, dry cough, tiredness, aches & pains, sore throat, conjunctivitis, headache, loss of smell & taste, rash on skin or discoloration of fingers or toes, difficulty breathing or shortness of breath, chest pain, loss of speech or movement.

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CRP

CRP a cytokine induced acute phase protein that increases in concentration as a result of inflammation, hence it is used as early marker or indicator of infection and inflammation.

The assay of CRP is more sensitive than ESR and leukocyte count, their levels rise and return to reference range more rapidly after the disease has subsided.

Why CRP test is important in Covid 19 prognosis?

Statistical studies among COVID 19 patients shows that CRP levels are highly correlated with the inflammation in the lungs and an increased CRP level is suggestive of poor prognosis. When a pathogen enters in body, inflammatory cytokines will be overproduced to fight against it and when it hyperactivates it can damage lungs and other internal organs. CRP levels are elevated in silent hypoxia (insufficient oxygen supply to body parts) results in trauma, shock, heart failure, heart attack and multiple organ failure .

During infectious or inflammatory disease states-

CRP levels rise rapidly within the first 6 to 8 hours.

Peak at is at up to 300 to 350mg/L after 48 hours .

CRP is raised by up to 50,000 times in acute inflammation.

CRP is one of the markers to evaluate the security of infection prognosis and therapeutic monitoring CRP is tested together with other clinical parameters for initial evaluation and follow up of Corona virus infection

D-DIMER

D- Dimer is one of the protein fragments produced when a blood clot gets dissolved in the body. It is not normally present in human blood plasma. D dimer tests are used to rule out the presence of an inappropriate blood clot (thrombus).

Why D dimer test is important in Covid 19 prognosis?

D Dimer is commonly evaluated in patients with Covid 19. In the disease condition inflammatory reactions triggered which result in increased production of inflammatory cytokines(cytokine storm) that activates coagulation process. When large numbers of clots break, the D- dimer levels elevate. Increase D dimer levels are also a predictor of developing acute respiratory distress in Covid 19, mentioning the probability of micropulmonary embolism especially in severe forms of Covid 19. Recently performed autopsies on 12 patients with Covid 19 show deep vein thrombosis in severe patients whereas some has pulmonary embolism as main pathological finding in two of these cases. That was directly stated in the clinical cause of death.

Studies on SARS Cov 2 revealed D dimer levels correlate with disease severity and are reliable prognostic marker for in hospital mortality in patients admitted for Covid 19.

Ferritin

Body cannot synthesize iron of its own and it absorbs iron from diet. Most of the absorbed iron is used for RBC production and the remaining is stored in form of ferritin. It is a major intracellular iron storage protein in all Organism. Why Ferritin test is important in Covid 19 prognosis?

When Corona virus enters the body, body over produces cytokines to fight against virus. This cytokine storm causes internal infection and inflammation which damage internal organs. When cells are damaged, ferritin stored inside is released in blood and resulted Hyperferritinemia. As per recent published guidelines longitudinal monitoring of a written during hospitalization may help to identify severe patients and predict the prognosis of Covid 19 towards hours clinical prognosis.

LDH (LACTATE DEHYDROGENASE)

LDH is an enzyme found in nearly all living cells. LDH catalyzes the conversion of lactate to pyruvate and back as it converts NAD⁺ and NADH. A dehydrogenase is an enzyme that transfers a hydride from one molecule to another. LDH is expressed extensively in body tissues, such as blood cells and heart muscle because it is released during this damage, act as marker of common injuries and diseases such as heart failure. LDH is an intracellular enzyme found in cells in almost all organ systems which catalyzes the interconversion of pyruvate and lactate, with concomitant interconversion of NADH and NAD⁺. The enzyme is composed by 2 major subunits (A&B) and is present in humans in five separate isoenzymes (LDH-1 in cardiomyocytes, LDH-2 in reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in kidneys & pancreas, LDH-5 in liver & striated muscle). Although LDH has been traditionally used as marker of cardiac damage since 1960s, abnormal values can result from multiple organ injury and decreased oxygenation with upregulation of glycolytic pathway. The acidic extracellular pH due to increased lactate from infection and tissue injury triggers the activation of metalloproteases and enhance macrophage mediated angiogenesis. Severe infections may cause cytokine-mediated tissue damage and LDH release. Since LDH is present in lung tissue (isoenzyme 3) patients with severe Covid-19 infections can be expected to release greater amounts of LDH in circulation as severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome, is the hallmark of the disease. However, the contribution of different LDH isoenzymes to the LDH elevation observed in COVID-19 has not been determined.

Procalcitonin

PCT which is 116-amino acid precursor of the hormone calcitonin, is normally synthesized and released by thyroid parafollicular C cells. However it can be synthesized in many extrathyroid tissues during bacterial infection which is mediated by increased concentration of tumour necrosis alpha (TNF alpha) & interleukin 6.

Objective:-

We aimed to provide overview of association of inflammatory markers with severity of Covid 19.

Methods:-

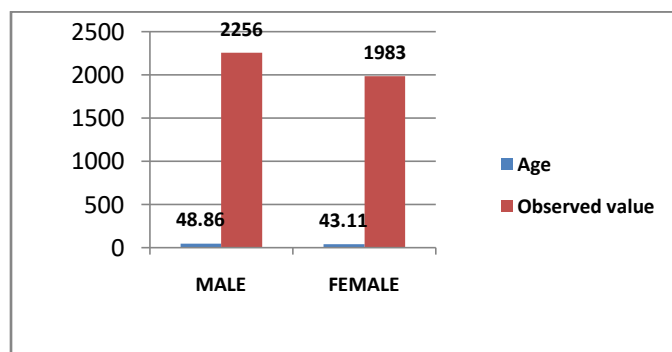
100 patients admitted in Shri Mahant Indresh Hospital Covid Ward with positive RT PCR. Serum samples taken and run on VITROS 5600 and reported for CRP, FERRITIN, LDH, Procalcitonin, D-dimer & TLC

Results:-

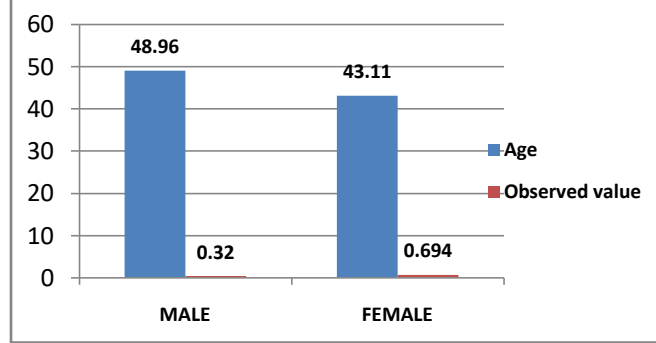
With 100 patients 34 were females & rest 66 were males. Out of which all parameters run on all patients. Mean age for males 48.86 ± 15.29 & Mean age for females 43.11 ± 16.21 . In all 6 parameters only 3 parameters CRP, LDH, Ferritin had significance in the study with p value < 0.01

Whereas rest 3 parameters TLC, D-dimer & Procalcitonin had non significant value. D-Dimer had p value 0.483. Procalcitonin P value 0.23. TLC p value 0.08. therefore these parameters in my study was not significant inflammatory markers in patients of Covid 19

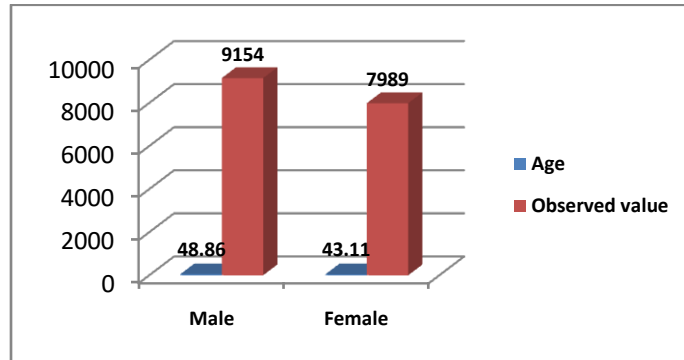
D-dimer	Male	Female			
Age	48.86 ± 15.29	43.11 ± 16.21	2.5804	0.0106	S(P<0.05)
observed value	2256 ± 2550	1983 ± 2937	0.7019	0.4836	NS(P>0.05)



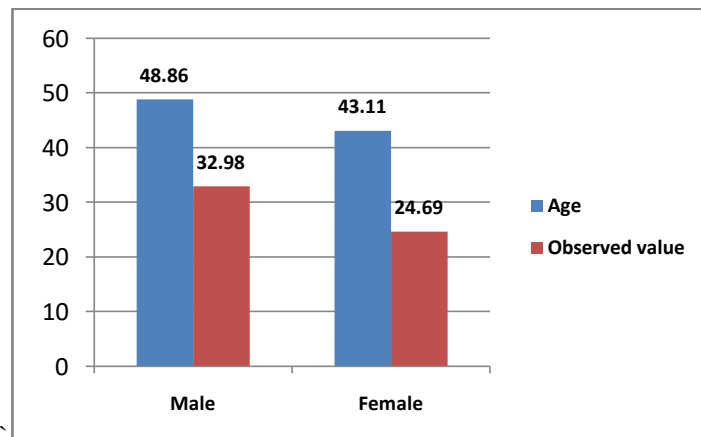
Procalcitonin	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	48.86±15.29	43.11±16.21	2.5804	0.0106	S(P<0.05)
observed value	0.320±1.434	0.694±2.780	1.1956	0.2333	NS(P>0.05)



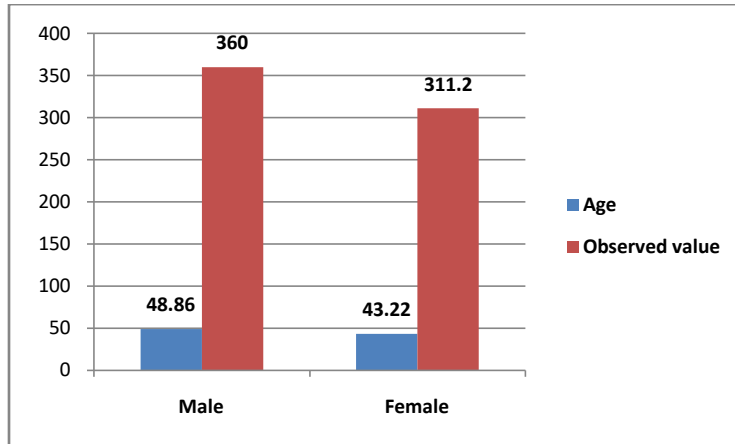
TLC	Male	Female			
Parameter	Mean±SD	Mean±SD	T value	P value	Significant
Age	48.86±15.29	43.11±16.21	2.5804	0.0106	S(P<0.05)
Observed value	9154±5555	7989±3821	1.7279	0.0856	NS(P>0.05)



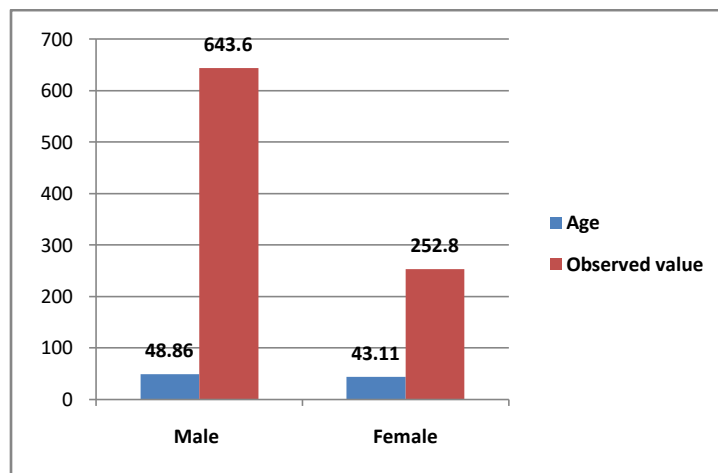
CRP	Male	Female			
Parameter	Mean±SD	Mean±SD	Tvalue	Pvalue	Significant
Age	48.86±15.29	43.11±16.21	2.5804	0.0106	S(P<0.05)
Observed value	32.98±26.30	24.69±23.44	2.3531	0.0196	S(P<0.05)



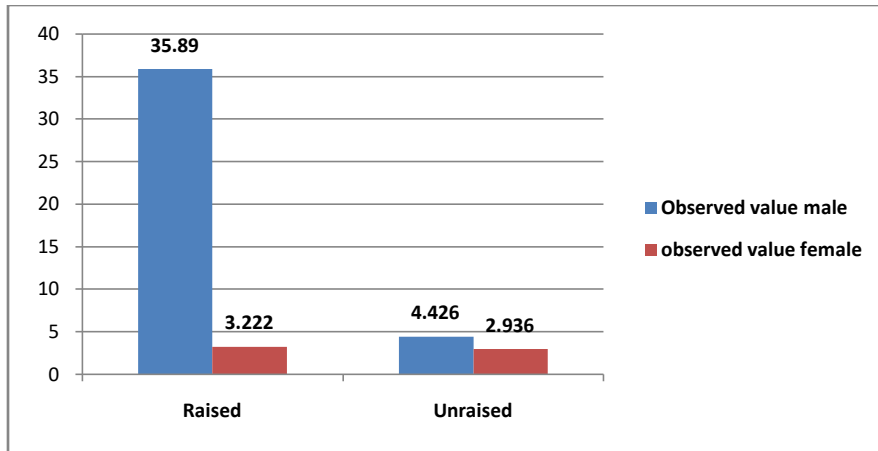
LDH	Male	Female			
Parameter	Mean±SD	Mean±SD	Tvalue	Pvalue	Significant
Age	48.86±15.29	43.11±16.21	2.5804	0.0106	S(P<0.05)
Observed value	360.0±188.7	311.2±165.4	2.5762	0.0107	S(P<0.05)



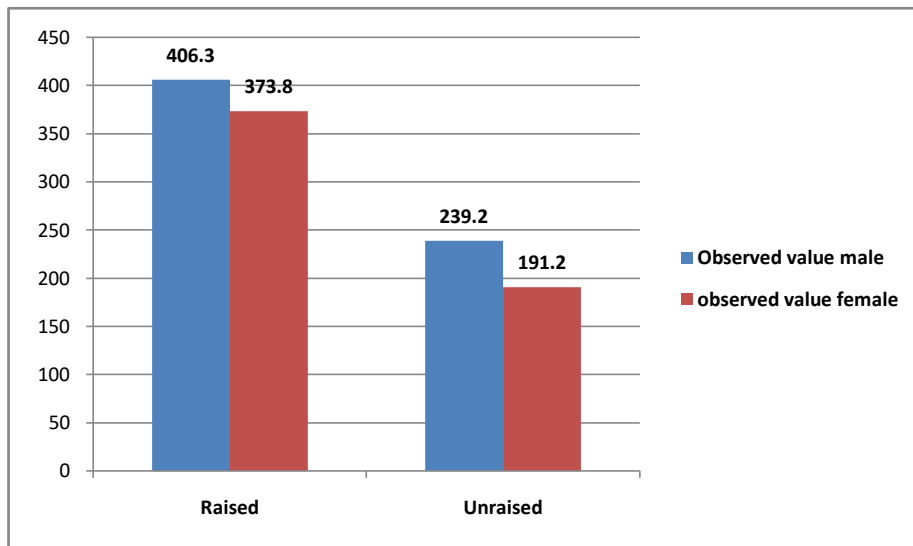
Ferritin	Male	Female			
Parameter	Mean±SD	Mean±SD	Tvalue	Pvalue	Significant
Age	48.86±15.29	43.11±16.21	2.5804	0.0106	S(P<0.05)
Observed value	643.6±830.4	252.8±250.1	4.5062	0.0001	S(P<0.05)



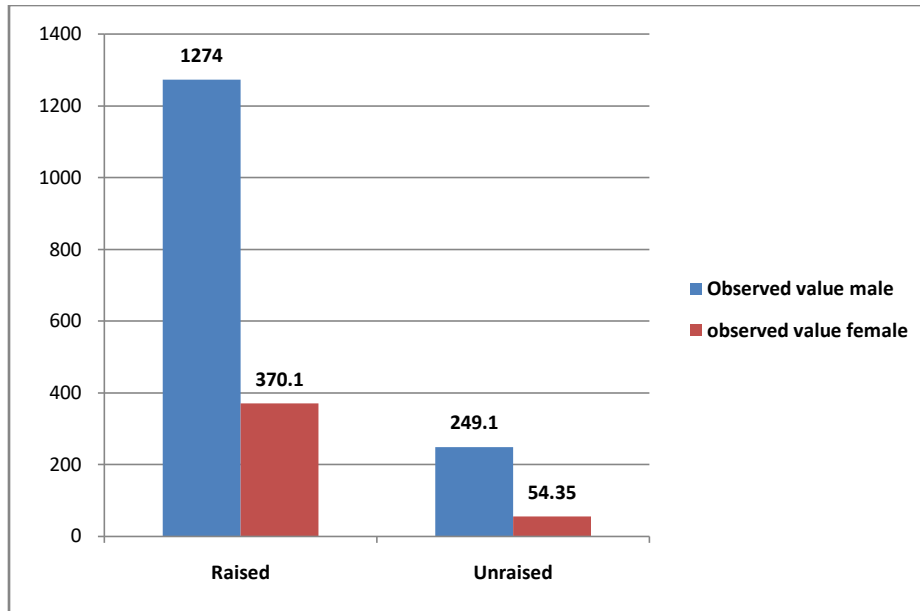
CRP	Raised	Unraised	T value	P value	significant
Observed value male	35.89±25.90	4.426±1.116	12.137	0.0001	S(P<0.05)
observed value female	3.222±22.75	2.936±1.246	0.1255	0.9002	NS(P>0.05)



LDH	Raised	Unraised	T value	P value	significant
Observed value male	406.3±174.6	239.2±173.5	6.7887	0.0001	S(P<0.05)
observed value female	373.8±169.9	191.2±54.56	10.2328	0.0001	S(P<0.05)



Ferritin	Raised	Unraised	T value	P value	significant
Observed value male	1274±1607	249.1±124.6	7.7495	0.001	S(P<0.05)
observed value female	370.1±248.5	54.35±3.907	12.7047	0.0001	S(P<0.05)



Discussion:

Covid 19 is hypothesized to be caused by cytokine release syndrome (CRS), an inflammatory immune response leading to organ failure(1-2). Severe Covid 19 & CRS have been linked to elevated levels of interleukin (IL) 6(3-5) which stimulates the liver to produce C- reactive protein(CRP) & fibrogen(6). In addition to CRP & fibrinogen, LDH & ferritin correlate with plasma IL-6 levels(7-8).

Clinical studies demonstrated that altered levels of some blood markers might be linked with the degree of severity and mortality of patients with Covid 19. Of these clinical parameters serum CRP has been found as an important marker that changes significantly in severe patients with Covid 19. CRP is a type of protein produced by liver that serves as an early marker for infection & inflammation. In blood the normal concentration of CRP is less than 10 mg/L, it rises rapidly within 6-8 hours & gives its peak in 48 hours from disease onset. Its half life is about 19 hours & its concentration decreases when inflammatory stage ends and patient is healing. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells. This binding makes active classical complement pathway of the immune system and modulates the phagocytic activity to clear microbes & damaged cells from organism. When inflammation resolves CRP concentration falls making it a useful marker for monitoring disease severity.

Significant increase of CRP was found with levels average 30-50 mg/L in patients with Covid 19. For example a study reported with more severe symptoms had an average CRP concentration of 39.4mg/L & patients with mild symptoms CRP concentration of 18.8mg/L(9). Another study mean conc. Of CRP was significantly higher in severe patients 46mg/L than non severe 23mg/L(10).

The utility of serum LDH in virus was first investigated by Zaman et al in 1988(11). They noticed that the level of serum LDH was useful as a marker of P.Jirovecii pneumonia in patients infected with the human immunodeficiency virus. Ede et al (12) reported that the severity of nasopharyngeal cellular injury during viral upper respiratory tract infection, as measured by LDH levels in nasopharyngeal secretions, was related to acute otitis media complication. They implied that there is positive correlation between levels of LDH & all cytokines (Interleukin IL- 1 β , IL-6 & tumour necrosis factor α).

The elevated serum LDH was observed in some studies about severe acute respiratory syndrome (SARS). Previous study of SARS data from 2003 found that lymphopenia, elevated LDH, AST & creatinine kinase levels were common in serious case(13). Liu et al(14) suggested that 58% of patients diagnosed with SARS presented elevated LDH on admission.

Ferritin is a key mediator of immune dysregulation especially under extreme hyperferritinemia, via direct immune suppressive & proinflammatory effects, contributing to cytokine storm. It has been reported to fatal outcomes by Covid 19 are accompanied by cytokine storm syndrome thereby it has been suggested that disease severity is dependant of cytokine storm syndrome. Many individuals with diabetes exhibit elevated serum ferritin levels and it is known that they face higher probability to experience serious complications from covid 19. In one study with 20 Covid 19 patients it was found that individuals with severe & very severe Covid 19 exhibited increased serum ferritin level, being serum ferritin in very severe Covid 19 group significantly higher than in severe group.

References :

- 1.Wang F, Yang Y, Dong K, Yan Y, Zhan S, Ren H, et al. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID 19 IN WUHAN, CHINA. *Endocrine Practice*. 2020; 26(6):668-674.pmid:32357072
2. Ciceri F, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *Crit Care Resusc*. 2020 ;22(2):95-97. Pmid:32294809
- 3.Lee DW, Gardner R, Porter DL, Louis C, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome . *Blood* .2014;124(2):188-195.pmid:24876563.
- 4.Teachey DT, Lacey SF, Shaw PA, Melenhorst J, Maude S, Frey N, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Cancer discovery*. 2016;6(6):664-679.pmid:27076371
5. Zhang T, Sun L, Feng R. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. *Chinese Journal of tuberculosis and Respiratory disease*. 2020;43:E040-E040.pmid:32241072
- 6.Rodriguez- Morales AJ, Cardona-Ospina JA, Gutierrez –Ocampo E, Villamizar- Pena R, Holguin-Rivera Y, Escaler- Antezana J, et al.Clinical , laboratory and Imaging features of Covid19: A systematic review and meta-analysis. *Travel medicine and infectious disease*.2020;34:101623.pmid:32179124
- 7.Chiappetta S, Sharma AM,Bottino V, Stier C. Covid -19 and the role of chronic inflammation in patients with obesity . *International Journal of Obesity*. 2020;44:1790-1792.pmid:32409680
- 8.Bozkurt B, Anguilar D, Deswal A, Dunar S, Francis G, HorwichT, et al. Contributory risk and management of comorbidities of hypertension , obesity, diabetes mellitus, hyperlipidemia and metabolic syndrome in chronic heart failure: a scientist statement from the American Heart Association. *Circulation*.2016;134(23):e535-e578.pmid27799274
- 9.Gao Y,Li T,HanM et al. Diagnostic utility of clinical laboratory data determinations for patients with severe COVID-19. *J Med Virol*.2020.10.1002/jmv.25770.
- 10.Mo P, Xing Y, XiaoY, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan , China. *Clin Infect Dis*.2020. 10.1093/cid/ciaa270.
- 11.Zaman MK,White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis* 1988;137:796-800.
12. Ede LC, O'Brien J, Chonmaitree T, et al. Lactate dehydrogenase as a marker of nasopharyngeal inflammatory injury during viral upper respiratory infection: implications for acute otitis media. *Pediatr Res* 2013;73:349-54.
- 13.Poutanen SM, Low DE, Henry B,et a. Identification of severe respiratory syndrome in Canada. *Radiology* 2003;87:1995-2005.
- 14.Liu CL, Lu YT, Peng MJ, et al. Clinical and laboratory features of severe acute respiratory syndrome vis-a-vis onset of fever. *Chest* 2004;126:509-17.

