ORIGINAL ARTICLE

The Acute Inflammatory Biomarkers - Are They Cost Effective and Real Time Early Predictors of Mortality in Acute Pneumonia? - A Prospective Observational Study

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ABSTRACT

Introduction: The CT chest and investigations like IL6 and TNF*a* are the most accurate blood biomarkers of inflammatory changes and can be used to stage the severity and outcome of acute pneumonia. . Getting all the above mentioned investigations in a financially poor patients is not always possible. There are not much studies to look for the association between early raise in serum acute inflammatory bio markers and the prediction of mortality in acute pneumonia. So this study is under taken to know the association between significant raise in serum acute inflammatory biomarkers like hs CRP, LDH, ferritin, NLR, WBCs count in predicting the mortality of acute pneumonia in comparison with the serum IL6,q-SOFA score and CT chest severity score. **Materials & Method:** All patients underwent standardized workup, including complete blood count, blood biochemistry, ferritin, hs-CRP, LDH,IL6,CT scan of chest ,q-SOFA score assessment and electrocardiogram. All the biochemical investigations were done on day 1 and day 5 of admission to the hospital. The patients were followed-up for the whole in hospital stay duration. **Results:** All the measured serum acute inflammatory bio markers, IL6, NLR, WBCs count, q-SOFA score and chest CT severity score were significantly elevated in patients with death due to acute pneumonia than the survived ones. [p value-0.01] **Conclusion**: This study proves that, the early raise in serum acute inflammatory biomarkers have got real and cost effective predictive value and are non-inferior to total WBCs count, NLR,IL6, q- SOFA score and chest CT severity score in assessing the mortality of acute pneumonia.

KEY WORDS: Acute Pneumonia, Acute inflammatory bio markers, CT scan of Chest, IL6, NLR (Neutrophils to Lymphocytes ratio), q-SOFA score, WBCs count.

Introduction

The acute pneumonia is one of the most common and important causes of hospitalization and death. The acute pneumonia is defined as the presence of any symptoms such as fever, cough, sputum,dyspnea and chest pain along with lung infiltration shadows on chest radiography.[1] Which happens due to infection of the lung parenchyma, that is acquired in a community, in a hospital or in a long-term care facility.[2]The specific etiological diagnosis of acute pneumonia is sometimes difficult because of negative laboratory findings.[3,4]We usually differentiate pneumonia from other non-infectious respiratory diseases by comprehensive evaluation including symptoms and signs, laboratory examinations, and the varied form of lung infiltrative shadows. However, some acute pneumonia patients, especially elderly patients, do not have cough, sputum, fever, and an elevated white blood cell count. Therefore, we usually perform blood tests for biomarkers to differentiate acute pneumonia from other non-infectious respiratory diseases. At present there are no serum biomarkers that could alone diagnose acute

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pneumonia, but the search for the ideal biomarker for pneumonia is ongoing, and multiple molecules are undergoing rigorous investigation.[5] Overprescribing of antibiotics could lead to an increase in the probability of infection with antibiotic-resistant organisms. Therefore, it would be beneficial to have either rapid detection of the causative pathogens or the availability of biomarkers that would signify a bacterial infection that requires antibiotic therapy.[6] Biomarkers have been defined as "a biochemical factor that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[5,6] An ideal diagnostic serum biomarker of acute pneumonia should get elevated, when there is viral, bacterial or fungal infections, to determine the need for appropriate drug therapy.[6] Many biomarkers have been developed and used for diagnosing acute pneumonia so far. However, all the biomarkers cannot be done in daily clinical practice due to financial and feasibility limitations.

The IL6(normal level is <7pg/ml) and q-SOFA score are significantly elevated in most of the subjects with Acute pneumonia with sepsis.[6] The q-SOFA score includes 3 components with score of one in each, they are impaired consciousness, respiratory rate of >22/min and systolic Blood pressure of <100mmhg. The q-SOFA score of >2 is taken as significant in sepsis for the assessment of severity.[1,2,7] In healthy adults, the normal hs-CRP concentration is usually less than 1 mg/L.[5–7] The secretion of hs-CRP starts within 4–6 hours, its level doubles every 8 hours and then reaches its maximum level within 36–50 hours. Once the stimulation is withdrawn, the hs-CRP level falls relatively quickly, with a half-life of 19 hours. Lactate dehydrogenase (LDH) is an enzyme implicated in the conversion of lactate to pyruvate in the cells of most body tissues and increased following tissue breakdown. The serum LDH levels serve as non-specific indicators of cellular death in many diseases.[7,8] Elevations of serum ferritin levels have been associated with a variety of infectious and noninfectious disorders. Elevations in serum ferritin level (>2 times the normal value) may occur with a variety of disorders as part of the acute-phase response. Acute-phase elevations in serum ferritin levels (>2 times the normal value) occur early and transiently.[9] The CT chest and investigations like IL6 and TNF*a*[5] are the most accurate blood biomarkers of inflammatory changes and parameters used to stage the severity and outcome of acute pneumonia.[9] Getting all the above mentioned investigations is not always possible for all the patients of acute pneumonia. There are not much studies to look for the association between acute early raise in serum inflammatory bio markers and the prediction of mortality in acute pneumonia. So this study is under taken to know the association between significant early raise in serum acute inflammatory biomarkers like hs-CRP, LDH, ferritin, NLR, WBCs count in predicting the mortality of acute pneumonia in comparison with IL6,q-SOFA score and CT chest findings.

Aims & Objectives

To study about the significance of acute inflammatory serum bio markers and their correlation with mortality of acute Pneumonia in comparison with IL6, q-SOFA score and CT scan of chest findings.

Materials & Methods

This was a prospective cohort study conducted on 180 subjects of acute pneumonia, who were admitted in icu at KR hospital, Mysuru from February 2021 to October 2022. The study was started after getting Ethical Clearance from MMC & RI, Mysuru Ethical committee with the number EC REG:ECR/134/Inst/KA/2013/RR-19.

In the present study, sample size was calculated using the formula $n= 4pq/d^2$.[1,10][1]

p = 32%, q = (100-p) = 68%, d = 11.25%.

- **Inclusion Criteria:** Patients in the age group of 18-80 year with acute pneumonia
- **Exclusion criteria**: Patients with-Connective tissue disorders, renal dysfunction, liver dysfunction ,autoimmune diseases, on steroids, any malignancy, and on anti-metabolites were excluded.

Demographic data, pneumonia symptoms and past medical histories such as comorbidities and active medications, were obtained by patient interviews. All patients underwent standardized workup, including complete blood count, serum ferritin, hs-C-reactive protein (hs-CRP), serum LDH, RFT, LFT, IL 6, CT Chest and electrocardiogram. The systolic BP of less than 90mmhg was taken as hypotension, Respiratory rate of >22/min was taken as Tachypnoea and the heart rate of more than >100/min was considered as Tachycardia.[1,2] The serum hs-CRP level of less than

1mg/L,[7] the LDH level between 105 to 333IU/L[8], the serum ferritin level between 11 to 336μg/L, normal serum IL6 was 0 to 43.5pg/ml, normal NLR was between 0.78 to 3.53 and normal WBCs count between 4000 to 11000/μl were considered as normal ranges in this study.[9] The common CT scan of chest findings in Acute pneumonia iirespective of the etiology were centrilobular nodules, ground glass opacities [GGO], and lobular areas of consolidation with bronchial wall thickening.[10] All the biochemical investigations were done on day 1 and day 5 of admission to the hospital. The CT chest was done on day 1 of the study in all patients and grading of severity was done by lobes involvement with scoring. There were 0 to 4 score with percentage of lobe involvement. The 0% with 0 score, <25% with 1 score, 25% to 50% with 2 score,50% to 75 % 3 score and >75 % with 4 score. Total 25 score were there, in that score between 0 to 8 was considered as mild pneumonia, 8 to 16 was moderate pneumonia and the score >16 was considered under severe pneumonia. The acute pneumonia staging was done based on clinical features and CURB 65 score [Confusion (Abbreviated Mental test score $\leq$ 8 or new disorientation in person, place, or time), raised blood **U**rea nitrogen (> 7 mmol/L), raised Respiratory rate ($\geq$ 30/min), low Blood pressure (diastolic $\leq$ 60 mmHg or systolic < 90 mmHg), Age $\geq$ 65 years], in to 3 stages, such as stage 1 with score<1, stage 2 with score of 2 and stage 3 with score of 3 and above.[11] T The q-SOFA score was recorded for all the patients on day 1 and day 5 of admission. The patients were followed up for the whole in hospital stay duration. The results were tabulated and studied to find the association between early elevated serum acute inflammatory bio markers, IL6,q-SOFA score and CT scan of chest severity score with the mortality due to acute pneumonia.

Statistical Analysis

Data obtained from the study has been entered in to a excel sheets and analyzed using SPSS(Statistical package for social sciences) software version 20. Descriptive statistics was used to calculate mean, Standard deviation, frequency and proportions of variables. The Anova and Chi square tests were used to look for the association between multiple variables. The Pearson Correlation coefficient was used to look for association between two variables.The p value of 0.05 was taken as significant.

Results

In the present study, the acute inflammatory serum biomarkers and their correlation with the clinical features, the severity and outcome of acute pneumonia was tabulated as follows

Predominantly female patients with the age of more than 60 years have got affected with the acute pneumonia. The salient features were fever, cough, breathlessness and Tachypnoea in majority of patients. The impaired consciousness and Hypotension were found in 35(19.44%) and 68(37.77%) patients respectively. All the acute inflammatory markers including serum IL6 were significantly elevated in most of the patients of acute pneumonia. [Table 1]

The features of acute pneumonia, like fever, cough, breathlessness, tachypnoea were found in majority of patients[p value 0.05]. The total mean WBCs count, serum IL6 and NLR (Neutrophils to Lymphocytes ratio) was also highly elevated in most of the patients of acute pneumonia. There was significant correlation between the main clinical features of acute pneumonia with that of elevated WBCs count, NLR, IL6, acute inflammatory biomarkers and chest CT severity score. [Table 2]

There was ascending and significant correlation between acute inflammatory serum biomarkers,IL6,NLR, Total WBCs count and CT chest findings with stages of acute pneumonia.[P value -0.01] [Table 3]

There was statistically significant association between elevated levels of acute serum biomarkers, IL6, q-SOFA score and mortality of acute pneumonia. [P value-0.01] The 45(25%) patients with high level of serum biomarkers, IL 6, q-SOFA score and CT severity score had mortality. [Table 4]

Discussion

This study was under taken to know the association between early elevated acute serum inflammatory biomarkers and the mortality of acute pneumonia in comparison with the elevated IL6, q-SOFA score and CT scan chest severity score. Indeed this study finds that, there was a strong and significant positive association between early elevated acute inflammatory serum biomarkers and the mortality of acute pneumonia in comparison with the elevated IL6, q-SOFA score and CT scan chest severity score of acute pneumonia. In this study, patients found

Table 1: Demographic characters, clinical and biochemical features of study subjects

Parameters		Numbers out of 180 (%)
Age (years)	<60.51±4.5	81(45)
	>60.51±4.5	99(55)
Gender	Male	88(48.88)
	Female	92(51.11)
Fever(>100F)		174(96.66)
Breathlessness		172(95.55)
Cough		In all
Hemoptysis		34(18.88)
Tachypnoea (>22 breaths/min)		178(98.88)
Hypotension (systolic BP<90mmhg)		68(37.77)
Altered consciousness		35(19.44)
Tachycardia (>100beats/min)		176(97.77)
$SpO_{2(\%)}$	<90	68(37.77)
	90-95	64(35.55)
	>95	48(26.66)
LDH (units/ml) Mean±SD	550.76±112.45	in all
FERRITIN (μg/l) Mean±SD	680.56±124.68	in all
hs CRP (mg/l) Mean±SD	12.65±3.40	in all
q-SOFA score - Mean±SD	2.5±0.8	In all
WBC scount/μl,mean ±SD	15630.15±1540.05	In all
Neutrophil to Lymphocytes ratio (NLR), mean±SD	4.68±1.21	In all
Serum IL6 pg/ml, mean±SD	158.68±46.45	In all
CT chest severity score-Mean± SD	17.31±6.39	In all

with the mean age of more than 60.51±4.5 years were 99(55%). The predominant gender involved in this study was female patients [92(51.11%)]. Which was compared with the study by Richardson S- where the median age was 63 years and in that 37.5% were female patients.[12] This shows that the acute pneumonia was very common in the elderly age group patients with the female preponderance. In this study the predominant features were fever, breathlessness, cough, tachypnoea and tachycardia in majority patients. Which in comparison to study by Mandell A. Lionel et al, where it found that, the fever, dyspnoea ,cough with sputum, tachypnoea and tachycardia were seen in majority of patients, irrespective of the etiology of acute pneumonia.[13] The acute severe espiratory failure with spo_2 of <90 was found in 68(37.77%) patients in this study. This shows that, the acute pneumonia could still be a one of the cardinal causes of acute respiratory failure. So high intensity life care, preferably respiratory ICU with close monitoring of patients was required to prevent mortality.[12,13] The serum biomarkers, such as serum hs-CRP, ferritin, LDH, IL 6, NLR, Total WBCs count and q-SOFA score were equally elevated along with the mean CT severity score of 17.31 in most of the patients. This shows that, the studied serum bio markers have got high sensitivity in assessing the acute inflammation along with assessing the severity, staging and mortality of acute pneumonia. The serum hs-CRP and IL6 were highly elevated in all stages of acute pneumonia and also it was showing significant correlation with the severity and mortality of acute pneumonia[p value 0.01]. This was compared with the study by Kim Woo Min et al, where the acute serum biomarkers like hs-CRP, Ferritin, LDH, total WBCs count, q-SOFA score and IL6 were elevated in most of the patients and were correlating with the mortality of acute pneumonia.[14] The serum LDH, serum ferritin, hs-CRP, IL6 and q-SOFA score levels were significantly elevated along with high mean CT severity score [17.31] in all stages of pneumonia and were persistently raised even after 5^{th} day of admission. This once again reiterates that, the serum biomarkers, IL6, q-SOFA score and CT severity score were correlating with the severity and stages of acute

Table 3: Comparison between the stages of acute pneumonia and the level of mean biomarkers, q-SOFA score and chest CT severity score

Main parameters level		Stages of acute pneumonia			P value
		Mild	moderate	severe	
At Day 1	Mean hs-CRP ± SD (mg/l)	14.65±3.6	18.11±2.4	22.12±3.7	0.01
	Mean LDH ± SD (units/l)	460.25±45.64	568.35±98.54	612.41±112.28	0.05
	Mean Ferritin ± SD (μg/l)	789.61±21.6	886.65±113.56	996.48±156.6	0.05
	Mean NLR ± SD	3.90±1.2	4.20±1.18	5.45±2.01	0.04
	Mean WBCs count ± SD (cells/μl)	12452.53±1233.12	14563.12±1634.54	16346.56±1452.23	0.05
	Mean IL6 ± SD (pg/ml)	116.23±25.45	168.46±65.78	289.76±76.84	0.01
	Mean q-SOFA score	1.5	2	2	0.01
	CT severity score	<8	8 to 16	>16	0.05
At Day 5	Mean hsCRP ± SD (mg/l)	16.65±4.6	22.11±2.51	24.12±4.7	0.01
	Mean LDH ± SD (units/ml)	660.25±45.54	768.35±88.54	814.41±102.28	0.05
	Mean Ferritin ± SD(μg/l)	989.61±124.06	986.65±113.26	1096.48±146	0.05
	Mean NLR ± SD (Neutrophils/ Lymphocytes ratio)	4.1±1.03	4.14±2.18	5.68±2.48	0.01
	Mean WBCs count ± SD (cells/μl)	13542.12±957.56	16453.56±1278.34	16789.78±1286.92	0.06
	Mean IL6 ± SD (pg/ml)	165.46±38.56	257.68±58.87	356.69±98.64	0.01
	Mean q-SOFA score	2	2.5	3	0.01

Table 4: Comparison between the level of serum acute inflammatory biomarkers, IL6, NLR, Total WBCs count, q-SOFA score and CT chest severity score with the in Hospital Outcome

	In Hospital Outcome (Mean Duration Stay of 10 Days)		P value
Biomarkers	In 135 (75%) survived Patients	In 45 (25%) Died patients	
Serum LDH (units/l) [mean ± SD]	451.31±41.34	618.34±45.51	0.06
Serum FERRITIN (μg/l) [mean ± SD]	414.12±34.62	780.64±67.81	0.05
Serum hs-CRP (mg/l)[mean ± SD]	09.12±3.44	15.34±3.69	0.01
Blood WBCs (count/μl) - mean ± SD	13452.53±1243.12	16564.45±1563.23	0.01
Blood NLR (Neutrophils / Lymphocytes ratio) -mean ± SD	3.89±1.24	5.48±2.43	0.01
Mean q-SOFA score	2	3	0.01
Serum IL6 (pg/ml) - mean ± SD	146.34±78.46	259.76±98.68	0.01
CT severity score - mean ± SD	12.51±04.23	22.12±8.56	0.05

Table 2: Comparison between clinical features and mean level of acute biomarkers, q-SOFA score and CT chest severity score

	The Number of Patients(%) With Mean Serum Biomarkers								
	LDH level – (Mean ± SD)	**FERRITIN level - (Mean ± SD)**	**hs-CRP level - (Mean ± SD)**	**NLR - (Mean ± SD)**	**WBCs count - (Mean ± SD)**	**IL6 level - (Mean ± SD)**	**q-SOFA score - Mean ± SD**	**CT score**	**P value**
Clinical Features	550.76±112.45 units/ml in numbers (%)	680.56±124.68μg/l in numbers (%)	12.65±3.4mg/l in numbers (%)	4.68±1.21(%)	15630.15±1540.03/cu.mm (%)	150.68±46.45pg/ml (%)	1.5±0.8	>16	
Fever	172(95.55)	174(96.66)	174(96.66)	174(96.66)	174(96.66)	174(96.66)	176(97.77)	78(43.33)	0.01
Cough	175(97.22)	171(95)	178(98.88)	178(98.88)	179(99.44)	179(99.44)	179(99.44)	84(46.66)	0.001
Breath-lessness	168(93.33)	172(95.55)	169(93.88)	172(95.55)	172(95.55)	172(95.55)	172(95.55)	84(46.66)	0.01
Tachy-cardia	176(98.88)	172(95.55)	169(93.88)	176(98.88)	176(98.88)	176(98.88)	178(98.88)	84(46.66)	0.05
Hypoten-sion	56(31.11)	68(37.77)	64(35.55)	68(37.77)	68(37.77)	67(37.22)	68(37.77)	78(43.33)	0.04
Tachyp-noea	176(97.77)	169(93.88)	178(98.88)	178(98.88)	178(98.88)	178(98.88)	179(99.44)	84(46.66)	0.01
SpO_2<95%	130(72.22))	126(70)	132(73.33)	132(73.33)	128(71.11)	132(73.33)	132(73.33)	84(46.66)	0.05

pneumonia, irrespective of etiology.[15] This was in comparison with the study by Tseng Cheng Chia et al, states that the estimated acute inflammatory biomarkers, such as CRP, procalcitonin, D-dimer, lactate, albumin, high-mobility group protein B1 (HMGB1), IL6, interleukin-8 (IL-8), interleukin-10 (IL-10) and CT severity scores on day 1 and day 3 of ICU admission were elevated n patients of acute severe pneumonia than the patients of mild pneumonia and its complications.[16] In this study the estimated acute serum biomarkers were correlating with mortality, irrespective of stages of acute pneumonia. This again reiterates that, the early elevated acute serum bio markers have got high predictive value in assessing the mortality of acute pneumonia. This was correlated with the study by Tseng Cheng Chia et al and Paula Ramírez et. al., states that the acute serum bio markers were serially elevated in patients of death due to acute pneumonia than the survived ones. Which once again reiterates that, the serum acute inflammatory biomarkers have got positive association with the severity and mortality of acute pneumonia.[16,17] The study by Nouvenne A states that, the serum acute inflammatory bio markers can be used in patients having multiple morbidity conditions, where they were having linear correlation with the severity of acute pneumonia and they could be used in segregating acute pneumonia patients.[18,19] As per studies by Agnello L.et.al. and Zhydkov A.et.al. the acute biomarkers like serum procalcitonin and CRP were correlating with severity and mortality of acute pneumonia. [20,21][20,21] The acute inflammatory serum biomarkers could be used in deciding the need of admission to ICU, deciding about the change in treatment protocol and the timing of discharge of pneumonia patients.[22–24] The study by Tsai Min Chih revealed that ,the salivary CRP could be used in predicting the severity of acute pneumonia in paediatric patients and it was correlating with the serum hs-CRP level.[25] As per the study of Liu Jinrong.et al., the serum biomarkers could be used to decide and chose appropriate antibiotics to treat the acute pneumonia.[26] According to the study by Fernandez JF., irrespective of etiology and stage, the serum markers were highly cost effective tool in managing the acute pneumonia.[27] So the high degree of acute inflammatory response along with elevated levels of serum acute biomarkers like hs-CRP, LDH, Ferritin, NLR and WBCs count plays a significant role in detecting the degree of damage caused to all organ tissues with multi organ dysfunction and deciding the type of medications

in comparison with IL6 and CT chest.[14,28] The serum hs-CRP level, IL 6 level, NLR and WBCs counts were more significantly elevated [p value-0.01] as compared to the serum ferritin and LDH level in patients of death due to acute pneumonia. The mean q-SOFA score was 3 and the mean CT severity score was 22.12 in patients of death due to acute pneumonia and it was positively correlating with all the early elevated serum acute inflammatory biomarkers including high NLR, WBCs count and IL6 level.

Limitations and suggestions

The sample size was limited, the studied acute inflammatory biomarkers needs to be correlated with highly sensitive and specific bio markers like TNF*a*. The patients follow up was limited only to, in hospital stay duration. Further more days of follow up was required to know the more plausible correlation between acute serum biomarkers and other causes of mortality like fibrosis of lung ,lung abscess and bronchiectasis etc.,

Conclusion

This study proves that, there is a irrefutable positive association between early elevated serum acute inflammatory biomarkers, Total WBCs count, NLR, IL6 level, q- SOFA score and chest CT severity score with that of mortality in acute pneumonia. This serum acute inflammatory biomarkers are significantly raised, as in comparison with the Total WBCs count, NLR, IL6 level, q- SOFA score and positive CT chest findings in acute pneumonia. So the early elevated serum acute inflammatory biomarkers are cost effective, feasible for all strata of patients and are noninferior to, NLR, Total WBCs count, IL6, q-SOFA score and CT scan of chest in predicting mortality of acute pneumonia.

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