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Original Article

Relation between Lipid Profile and Outcome of Pneumonia with Sepsis

Mokhles Abdelfadil Ibrahim Zineldin[1*]; Ibrahim Fathi [1]; Ali Shaaban [1]; Sherif Ibrahim Elghannam[2]

[1] Department of Chest Diseases, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.
[2] Department of Clinical Pathology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.

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*Corresponding author

Email: mokhlesabdelfadil@gmail.com

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Abstract

Background: Lipid changes in sepsis is addressed. However, high density lipoprotein is extensively studied. Other lipids are poorly studied. In addition, the lipid profile changes in sepsis due to pneumonia is poorly investigated, especially its relation to in-hospital mortality.

The aim of the work: This work aimed to examine the changes in lipid profile, amongst others, in sepsis-related mortality due to pneumonia.

Patients and methods: Eighty patients with confirmed diagnosis of pneumonia with sepsis were included. They followed up till their discharge and then categorized into survivors [n=54] and non-survivors [n=26]. The laboratory, clinical, and radiological data were compared between both groups. In particular, the levels of lipid profile were estimated and correlated with mortality.

Results: The mortality rate among study subjects was 32.5%. Mortality was significantly associated with older age, higher smoking index and admission to intensive care unit [ICU]. The mean age of survivors was 56.15±9.69 year, compared to 66.73±6.24 years for non-survivors, while the [Median [IQR]] smoking index was 525.0[612.5] and 175.0[472.5] in non-survivors and [survivors], respectively. Furthermore, the lipid profile revealed significant reduction of high- and low-density lipoproteins in non-survivors than Survivors [49.23±4.10, 106.61±4.48 vs 55.29±3.69 and 131.16±7.16, respectively]. Similarly, cholesterol was significantly reduced in non-survivors than Survivors [140.50±5.87 vs 157.77±8.90, respectively]. Mortality was also significantly associated with higher liver enzymes, C-reactive protein CRP, neutrophil percentage, neutrophil-lymphocyte ratio [NLR] and serum creatinine, while it was associated with a significant reduction of serum albumin and lymphocyte percentage.

Conclusion: Serum cholesterol, Low density lipoprotein and high-density lipoprotein levels, but not triglycerides significantly reduced in non-survivors with pneumonia-related sepsis when compared to survivors. It can be used as predictor indicators for mortality, beside others in those patients.

Keywords: Sepsis; Pneumonia; Mortality; Prognosis; Lipids.

INTRODUCTION

Pneumonia is defined as an inflammatory disease that affects the lung alveoli. Clinically, it presents by a combination of productive or dry cough, chest pain, fever and dyspnea. It varies greatly in severity and it is mainly due to viral or bacterial causes. However, other microbes are able to cause pneumonia. It is still a leading cause of morbidity and mortality all over the world [1].

Sepsis and pneumonia are responsible for significant mortality and morbidity. A complex relationship of immune-molecular pathways is shared by both sepsis and pneumonia, leading to similar and overlapping disease manifestations. Sepsis may be a result of unmanaged pneumonia. Otherwise, sepsis from other origin than the lung, may be complicated by pneumonia [2].

The levels of plasma lipids have long been linked to the pathogenesis of atherosclerosis and coronary heart disease [CHD] [3]. However, there is increasing interest in their role in host immunity [4].

In infections [bacterial, viral or parasitic], altered plasma lipids have been reported, and the changes are correlated with the severity of infection [5, 6].

Recently, significant advances have introduced in diagnosis and treatment of sepsis. However, it remains an intractable medical condition with high morbidity and mortality rates [7].

Early diagnosis and timely treatment are pivotal in reduction of sepsis-associated morbidity and mortality [8,9].

Blood culture remains the golden standard for the diagnosis of sepsis and causative organisms. However, it needs a time with false negative results. Thus, its clinical usage is weakened especially in severely acute cases. The development of new biomarkers to help the early diagnosis and consequently timely and proper initiation of antimicrobial therapy is crucial [10].

Previous study demonstrated changes in serum lipoprotein concentrations sepsis in adults, and it can be used as a prognostic factor in sever sepsis [11].

In addition, lipids and lipoprotein are increasingly identified to play an integral role in pathogenesis of immunity and infection [12].

This was studied in experimental as well as observational epidemiological studies. All of these recognized changes in lipids and lipoproteins in sepsis. Others studied associations between certain lipids and its association with sepsis [13-16]. However, the association between lipid profile as well as other laboratory indicators with sepsis-associated mortality is poorly studied. In addition, studies about the link between pneumonia-associated sepsis, in particular, and its relation to associated mortality are scarce.

In addition, HDL is the widely studied lipid molecule in sepsis. Other molecules are poorly studied in patients with sepsis. The prognostic significance of lipid profile in sepsis due to pneumonia and its associated in-hospital mortality remains unclear. Thus, the current work was designed to investigate the possible changes in lipid profile and its association with mortality-related sepsis due to pneumonia.

PATIENTS AND METHODS

Patients: This study included 80 patients with confirmed sepsis due to pneumonia. They were selected from the chest diseases' department, Al-Azhar University Hospital [New Damietta]. The study completed during the duration between January 2023 and January 2025.

Inclusion criteria:

Inclusion criteria: Severe pneumonia with sepsis who need hospital or respiratory [intensive] care unit admission. This was defined as having one major or three minor criteria.

The major criteria include 1] sepsis or septic shock requiring vasopressors, 2] respiratory failure requiring mechanical ventilation. On the other side, minor criteria include 1] respiratory rate ≥ 30 or more breaths per minute, 2] PaO_2/FIO_2 ratio ≤250, 3] multilobar infiltrates, 4] confusion, 5] uremia, 6] leukopenia [WBC < 4000 cells/dl], 7] thrombocytopenia [platelet count < 100,000/µl], 8] hypothermia, and 9] hypotension.

For the purpose of the study, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This aimed to emphasize the primacy of the non-homeostatic host response, the potential mortality, and the need for urgent diagnosis.

Exclusion criteria

These criteria included 1] Other chest diseases, 2] previous diagnosis of dyslipidemia, and 3] patients received therapy for lipids.

Ethical aspects:

The study protocol was submitted, evaluated and accepted by the local research ethics committee of Damietta Faculty of Medicine, Al-Azhar University, New Damietta, Egypt. In addition, an informed consent had been obtained from the patient him/her-self or his/her legal representative. This was obtained after full explanation of the study protocol with preservation of all patients' rights for proper treatment and withdrawal at any time without effect on his/her treatment plan. Collected data were anonymized and used only for the purpose of this research.

Methods

Patients were evaluated in a standard manner. This included history taking, physical general and local chest examination. This was followed by imaging and laboratory workup.

The imaging workup consisted of plain X-ray chest [for all included subjects] and chest CT exam for selected patients.

The laboratory investigations, however, included complete blood count [CBC], liver enzymes [ALT, AST], serum albumin and serum creatinine levels. In addition, lipid profile [triglycerides, total cholesterol, low-density lipoprotein and high-density lipoproteins] was determined.

Blood Sampling and analysis:

Blood samples were drawn via an indwelling arterial catheter or via venous puncture at admission. The total cholesterol [normal: 100–220mg/dL], HDL [normal: 40–86mg/dL], TG [normal: 44–240mg/dL],

and LDL [normal range: 70–169mg/dL], were measured using the available commercial kits with an automated analyzer [Hitachi 7600-200-DDP, Hitachi Ltd., Tokyo, Japan], in our lab.

Statistical Analysis:

The normally distributed continuous variables were summarized by their arithmetic means and standard deviations. Otherwise, medians and interquartile ranges [IQR] were used to summarize non-normally distributed data. Then groups were compared by Student's t-test or Mann-Whitney's *U* test, depending on the normal or non-normal distribution, respectively.

In addition, categorical variables were summarized by their relative frequencies and percentages from each group [survivors and non-survivors] and the possible association was examined using Pearson's Chi-squared or Fisher's exact tests, as appropriate. P value < 0.05 was set as the significant level from the statistical point of view. Finally, all these analyses were performed using Microsoft Excel [Microsoft Inc., USA] and statistical package for social science, version 16 [SPSS, Chicago, IL, USA].

RESULTS

The current work included a total of 80 patients admitted to respiratory care unit or respiratory medicine department due to pneumonia with sepsis. All were followed up till discharge and mortality was determined. It was reported for 26 patients [32.5%]. Then, laboratory and clinical data were compared between the survivors and non-survivors.

Mortality was significantly associated with the older age, higher smoking index and admission to intensive care unit [ICU]. For instance, improvement was reported for patients aged 32 to 72 years [mean±SD; 56.15±9.69] compared to 66.73±6.24 years for non-survivors' patients. In addition, the [Median [IQR]] smoking index was 525.0[612.5] and 175.0[472.5] in non-survivors' and improved [survivors] patients, respectively [Table 1].

Finally, ICU admission was significantly higher in non-survivors' than survived cases [80.8% vs 20.4%, respectively]. Otherwise, no significant association was reported between outcome and patient gender, smoking grade and clinical manifestations [Table 1].

In the current work, mortality was significantly associated with multi-lobar consolidation [detected by chest- X- ray] Lower oxygen and carbon dioxide tension [Table 2].

The lipid profile showed that, there was significant reduction of HDL and LDL in non-survivors than Survivors [49.23±4.10, 106.61±4.48 vs 55.29±3.69 and 131.16±7.16, respectively] [Table 2].

In addition, there was a significant reduction of cholesterol in non-survivors than Survivors [140.50±5.87 vs 157.77±8.90, respectively] [Table 2]. Other laboratory investigations showed that, mortality was significantly associated with higher AST, ALT, CRP, and neutrophil percentage, neutrophil-lymphocyte ratio [NLR] and serum creatinine, while it was associated with a significant reduction of serum albumin and lymphocyte percentage [Table 2].

Table [1]: Comparison between Survivors and non-survivors regarding patient demographics, clinical manifestations and admission.

Variable	Measures	Survivors [n=54]	Non-survivors [n=26]	Test	P value
Age [years]	**Mean±SD**	**56.15±9.69**	**66.73±6.24**	***5.08***	***<0.001****
	Min. – Max.	**32-72**	**52-80**		
Sex [n,%]	Male	35[64.8%]	20 [76.9%]	1.20	0.31
	Female	19 [35.2%]	6 [23.1%]		
Smoking index	**Median [IQR]**	**175.0[472.5]**	**525.0[612.5]**	**2.72**	**0.008***
Smoking grade [n,%]	Non-smokers	25[46.3%]	7[26.9%]	6.61	0.085
	Mild [index ≤200]	4 [7.4%]	1 [3.8%]		
	Moderate [400>index>200]	6 [11.1%]	1 [3.8%]		
	Severe [index >400]	19 [35.2%]	17 [65.4%]		
Symptoms and/or signs [n,%]	Fever	54[100.0%]	26[100.0%]	-	-
	Cough	54[100.0%]	26[100.0%]	-	-
	Dyspnea	45[83.3%]	20[76.9%]	0.47	0.49
	Chest pain	7[13.0%]	4[15.4%]	0.09	0.77
	Wheeze	0[0.0%]	0[0.0%]	-	-
Admission [N,%]	Ward	**43[79.6%]**	**5[19.2%]**	**26.67**	**<0.001***
	ICU	**11[20.4%]**	**21[80.8%]**		

Table [2]: Radiological and laboratory investigations

Variable	Measures	Survivors [n=54]	Non-survivors [n=26]	Test	P value
Chest X-ray [n,%]	Lobar Consolidation	**41[75.9%]**	**6[23.1%]**	***20.22***	***<0.001****
	Multi-lobar consolidation	**13[24.1%]**	**20[76.9%]**		
Hemoglobin [g/dl]	Mean±SD	9.75±0.42	9.65±0.44	0.96	0.33
WBCs x [10^3/cc]	Mean±SD	15.07±1.99	15.95±1.93	1.87	0.065
Platelets x [10^3/cc]	Mean±SD	189.94±19.51	186.88±23.63	0.61	0.54
PO2	Mean±SD	***69.55±2.96***	***55.23±3.25***	***19.58***	***<0.001****
PaCO2	Mean±SD	***42.64±1.03***	***37.65±2.38***	***13.12***	***<0.001****
HDL	Mean±SD	***55.29±3.69***	***49.23±4.10***	***6.62***	***<0.001****
LDL	Mean±SD	***131.16±7.16***	***106.61±4.48***	***15.99***	***<0.001****
TG	Mean±SD	83.27±5.10	85.34±8.93	1.31	0.192
Cholesterol	Mean±SD	***157.77±8.90***	***140.50±5.87***	***8.98***	***<0.001****
AST	Mean±SD	***30.29±5.33***	***54.23±9.92***	***14.05***	***<0.001****
ALT	Mean±SD	***33.77±8.23***	***46.96±6.10***	***7.25***	***<0.001****
Albumin	Mean±SD	***4.07±0.15***	***3.64±0.18***	***11.07***	***<0.001****
CRP	Mean±SD	***48.51±5.77***	***56.65±9.59***	***4.72***	***<0.001****
Neutrophil %	Mean±SD	***51.44±6.91***	***64.23±9.87***	***6.71***	***<0.001****
Lymphocyte %	Mean±SD	***25.80±6.53***	***14.91±4.78***	***7.56***	***<0.001****
NLR	Mean±SD	***2.14±0.71***	***4.70±1.58***	***9.99***	***<0.001****
Creatinine	Mean±SD	***1.46±0.34***	***1.75±0.36***	***3.62***	***0.001****
Uric acid	Mean±SD	5.16±0.71	5.06±0.56	0.65	0.52

DISCUSSION

Sepsis is a complication of different severe infections. It is associated with higher rate of multi-organ failure and mortality [17]. In addition, sepsis has additional long-term consequences, mainly impaired quality of life [18].

The relationship of lipid profile [mainly high-density lipoprotein cholesterol] and sepsis and its outcome is an area of research and therapeutic interest. However, the previous studies dealing with the topic are of experimental origin. In addition, epidemiological clinical studies reported on the broad topic of sepsis regardless its origin. Thus, the current work was designed to examine the association between lipid profile and pneumonia-associated sepsis. Eighty patients with pneumonia were included. Their outcome regarding mortality was used to categorize patients into two groups, the survived [improved; n=54] and non-survived [n=26]. Thus, the mortality rate in the current work was 32.5% reflecting the higher mortality rate associated with sepsis, regardless its origin. In addition, the mortality due to sepsis-associated pneumonia was significantly associated with older age, higher smoking index, admission to ICU, multi-lobe involvement, lower oxygen and carbon dioxide tensions, lower HDL, LDL, cholesterol, serum albumin and lymphocyte percentages. However, at the same time, it is associated with significantly higher liver enzymes, CRP, neutrophil percentages, NLR, and serum creatinine. These laboratory changes reflecting the multi-organ effect of sepsis.

Regarding clinical data, the results of the current work agree with **Chang *et al.*** [19] who reported that, when comparing deceased with survived patients, they found significant differences regarding age. For instance, the average age of deceased was 69 years, compared to 43 in surviving.

The results of the current work are in line with previous studies. For instance, **van Leeuwen *et al.*** [20] reported that, HDL cholesterol is rapidly dropped in patients suffer from sepsis. Others reported that, HDL-C levels are significantly associated with early onset of sepsis, increased risk of multi-organ failure and higher mortality [21, 22]. The lower levels of HDL are explained by it action in sepsis. It binds and neutralizes lipopolysaccharide [endotoxin], a mediator of sepsis to increase its clearance [23, 24]. This was confirmed in experimental models, where the usage of reconstituted HDL to treat sepsis is associated with a protection from organ injury and increased survival rate [13,25]. In addition, a clinical study by **Madsen *et al.*** [14] showed that, the reduced HDL-C was a strong predictor for higher risk of infection, worse outcome and higher mortality.

In addition, the lower levels of HDL may be related to its anti-inflammatory proprieties. It can suppress the tumor necrosis factor-α [TNF-α]–induced vascular cell adhesion molecule-1 [VCAM-1] expression at endothelial cells [26]. In addition, it can attenuate the endothelial dysfunction and systemic inflammatory response by the blunting of transcriptional factors [e.g., nuclear factor Kappa-B] [27, 28].

It had been reported that, the dysregulation of immune response and multi-organ failure [reflected in the current work by multiple changes in laboratory workup] are recognized as the primary causes of death. However, the wide variations of clinical manifestations and outcome in sepsis suggest other factors in pathology [29]. This could explain the poor outcome and higher mortality [30]. This reflected the value of the current

work, searching the potential role of lipid profile changes in pneumonia-associated sepsis.

Morin *et al.* [31] and Cao and Huang [32] showed that HDL significantly reduced in patients with sepsis. This may be due to the fact that, sepsis initiates a systemic inflammatory response, with subsequent release of inflammatory cytokines [e.g., TNF-α, and interleukin-6 [IL-6]], which inversely correlated with HDL **[33],** indicating that inflammatory mediators may indirectly decrease synthesis of HDL by inhibition of hepatic lipid metabolism.

Other proposed mechanisms lead to reduction of HDL cholesterol in sepsis include the consumption of HDL, hemodilution, capillary leakage or reduced synthesis by the liver, especially in cases of sepsis-associated liver dysfunction **[11,34,35].**

Results of the current work agree with **Hofmaenner *et al.* [36]** who showed a significant association between a hypocholesterolemia [total, HDL-C, and LDL-C] at ICU admission and mortality in patients with sepsis. However, there was no significant association between mortality and triglycerides.

Reduction of serum lipids are a well-recognized feature in critical illnesses including sepsis, trauma, and burns **[37, 38]. Golucci *et al.* [39]** included patients with systemic inflammatory response syndrome [SIRS] and sepsis reported changes in lipids and demonstrated profound alterations in total cholesterol, and HDL-C and LDL-C levels. However, the authors did not check the associations between mortality and lipid profiles and also included conditions other than sepsis.

In the current work, no significant association was found between outcome and patient gender. However, overall women are lower than men. Females represented 31.25% of all included patients. This is in line with previous epidemiological studies revealed that, the incidence of sepsis was lower in women than men **[40,41].** In addition, others reported that, the association between clinical outcome and gender is inconsistent with no clear data on the effect of gender on sepsis and vice versa **[42-44].** However, the gender distribution in the current work is in line with **Chang *et al.* [19]** who included 265 patients with sepsis, 104 [39.2%] were female, and 161 [60.8%] were males.

The smoking index was significantly associated with mortality in pneumonia-related sepsis, in the current study. This is in line with previous studies indicating that, smoking is associated with adverse outcome of sepsis **[45,46].** However, other researchers could not find this association **[47].** Interestingly, when we graded smoking into [mild, moderate, severe] according smoking index, the association between mortality and smoking grade did not reach statistical significances. Thus, the grading and analytical methods could be responsible for contradictory results. In addition, the sample size and inclusion criteria between different studies may explain this contradiction.

Conclusion: lipid profile [serum cholesterol, Low density lipoprotein and high-density lipoprotein levels, but not triglycerides] significantly reduced in non-survivors with pneumonia-related sepsis when compared to survivors. It can be used as predictor indicators for mortality, beside others in those patients. However, due to study limitations [small sample size and single center nature], the results must be treated cautiously and future large scale, multi-center studies are warranted.

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