Role of C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) in diagnosis of Pharyngitis in Cirrhotic Patients: A Trial to end of Antibiotics Abuse

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Abstract

Background: Patients with cirrhosis are at high risk for the development of infections, acute pharyngitis is probably the most common infection presented to the everyday clinic.

Objectives: To evaluate the role of CRP and ESR, in differentiation between bacterial and viral pharyngitis in patients with liver cirrhosis.

Patients and methods: This study conducted on 80 participants. Group A: (cirrhotic patients) involve forty patients, twenty of them presented to the clinic with acute pharyngitis and the other twenty have no signs or symptoms suggestive acute pharyngitis. Group B: (immune-competent [non cirrhotic] patients) includes forty patients. Half of them have acute pharyngitis and the other half is clinically free. Acute viral and bacterial pharyngitis was differentiated clinically. ESR, CRP and throat culture were done for all participants

Results: The mean ESR value in viral and bacterial pharyngitis-infected hepatic patients was 50.55 ± 36.89 and 38.35 ± 28.69 respectively (p=0.242). The mean CRP value in viral and bacterial pharyngitis-infected hepatic patients was 47.38 ± 9.58, and 53.91 ± 36.37 respectively (p=0.684). The mean ESR level in the bacterial and viral non-hepatic infected patients were 32.35 ± 2.16 and 19.25 ± 10.72 respectively with significant p-value (P=0.0001). The mean CRP value in viral and bacterial non-hepatic infected patients were 3.53 ± 3.01 and 20.35 ± 18.81 respectively with significant p-value (P=0.0001).

Conclusion: In immunocompromised patient complaining of sore throat must undergo throat culture to identify the organism and apply the most suitable treatment to avoid antibiotic abuse, misuse and bacterial resistance.

Keywords: CRP; ESR; Liver cirrhosis; Pharyngitis**.**

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Introduction

Cirrhosis is one of the leading causes of death worldwide especially with decompensated cirrhosis; where the overall five year survival is about 15% **(Mokdad et al., 2014)**.

Patients with cirrhosis are at high risk for the development of infections, due to multiple factors such as increase permeability of the intestinal wall, bacterial transmission and a state of immune-compromising **(Piano et al., 2018)**.

Acute pharyngitis is probably the most common and controversial infection that presented to everyday clinic and may be related to bacterial causes as Streptococcus pyogenes or virus pathogen (**Susan et al., 2018)**.

Pharyngitis is common all over the world, more commonly in temperate climates.According to National Ambulatory Medical Care Survey reports, annually; about two hundred patients every one thousands of population presented with upper respiratory tract infections, involving acute pharyngitis, in the United States (**Peltola, 1982**; **Gonzales et al., 2001**).An upper respiratory tract infection usually presents with increased body temperature, malaise, headache, coryza and sore throat. Difficult to be distinguished clinically **(Breese et al., 1954)**.

There are many agents which cause pharyngitis with Viral infections accounting for approximately 70% of all pharyngitis, and bacteria causing 20 to 30% of pharyngitis but group A beta-haemolytic streptococcus need physician special concern due to its spreading and complication including acute rheumatic fever, toxic shock syndrome and acute glomerulonephritis so a etiological differential diagnosis for pharyngitis must be done **(Stillerman et al., 1961 ; Somro et al., 2011; Hung et al., 2013)** as presented in **(Table 1).**

Table1. Causes of pharyngitis (Hung et al. 2013)

Bacteria Corynebacterium other spp	Arcanobacteriumhaemolyticum, CorynebacteriumdiptheriaeHaemophilusinfluenzae, Legionella pneumophilia ,Neisseria gonorrhoeae, Neisseria meningitides Streptococcus pyogenes (group A beta-hemolytic) ,Streptococcus spp. (groups B, C and G) ,Treponemapalidium and Yersinia enterolitica
Fungal/rickettsial/intracellular organisms	Candida spp. ,Mycoplasma pneumoniae, Coxiellaburnettii and Chlamydia pneumoniae
Viruses	Rhinovirus ,Adenovirus, Coronavirus, Coxsackie A virus ,Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus and Human immunodeficiency virus-1
Parainfluenza	Influenza A and B ,Measles, Reovirus and Respiratory syncytial virus

There are other factors that may play a role in occurrence of sore throat e.g. allergies, dust and smoke, post nasal discharge and low mucosal humidity (**Hung et al., 2013)** Respiratory tract infection in patients with liver cirrhosis reported in nearly 20% of patients with mortality rates about 40% **(Jalan et al., 2014)**.

Respiratory tract infection in cirrhotic patients has many consequences including acute on chronic liver cell failure, different organ failure, sepsis, prolonged hospital stay, and increase mortality **(Preveden, 2015)**. There are very few studies of viral upper respiratory tract infection in cirrhotic patients **(Fernández et al., 2012)**.

Abuse of antibiotics in the management of upper respiratory tract infection without differentiation between viral and bacterial causes led to the development of multidrug-resistant microorganisms in this group of patients **(Klímová et al., 2016)**. This is important, as the choice of suitable treatment could overcome the resistance to antibiotics **(Mcfarlane, 1998)**.

The clinical management of acute pharyngitis remains controversial. The clinical diagnosis is not specific. Laboratory data can be deceptive and sometime misconceiving. Epidemiological evidence suggests that the complexities and the controversies of these infections remain uncontrolled **(Dissanayake, 2011)**.

The erythrocyte sedimentation rate (ESR) is used for detecting acute and chronic inflammation and is one of the most common and traditional laboratory tests in the world. It is simple, nonspecific test, easy to perform, inexpensive and is used today as a routine test worldwide that used as disease indicator and to follow up treatment as in rheumatic disease **(Markanday, 2015)**.

C-reactive protein is a pentameric protein synthesized by hepatocytes. CRP production is stimulated by cytokines; particularly IL-6, IL-1, and tumour necrosis factor in response to infection or tissue inflammation. CRP as an inflammatory marker, it appears and reaches high levels at early stages of inflammation.

It also returns to normal levels more quickly upon resolution of stimuli **(Sproston and Ashworth, 2018)**. Microbiological culture is the best test to establish an aetiological diagnosis in pharyngitis but is time consuming **(Shulman et al., 2012)**.

The question therefore arises whether inflammatory marker such as (CRP) and (ESR) can differentiate bacterial from viral pharyngitis in a trial to decrease antibiotics abuse especially in immunocompromised patients such as cirrhotic patients.

Patients and method

This is a case-control study conducted in ENT and Tropical Medicine & Gastroenterology outpatient clinic in South Valley and Assiut University Hospitals during period from 1st April 2022 till 1st June 2022. Patients divided to two main groups A and B.

Group A:(cirrhotic patient) involve forty patients. Twenty of them presented to clinic with acute pharyngitis (infected hepatic) and the other twenty have no signs or symptoms suggestive acute pharyngitis (cirrhotic non-infected patients) (control hepatic). Group

B: (immune-competent [non cirrhotic] patient) includes forty patients. Half of them have acute pharyngitis (infected non hepatic) and other half clinically free (control non hepatic)

Acute pharyngitis in infected patient differentiated and divided to viral and bacterial pharyngitis clinically by using the Infectious Diseases Society of America (IDSA) categories [19] Category 1 (probable viral pharyngitis) with conjunctivitis, coryza, cough, diarrhoea, viral-like exanthemas. Category 2 (suggestive of possible bacterial pharyngitis) with fever of more than 38.5 C, tender anterior cervical lymph nodes, headache, petechiae of the palate, abdominal pains, or sudden onset (<12 hr).ESR, CRP and throat culture were done for the eighty patients and comparison between the clinical data, laboratory finding and throat swab and cultures was done.

The study protocol was approved by Ethics Committee of Qena Faculty of Medicine South Valley University and written informed consent was obtained from all included subjects.

Statistical analysis

Data entry and data analysis were done using SPSS version 22 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation, median and range. Chi-square test and Fisher Exact test were used to compare between qualitative variables. Independent samples t-test was used to compare quantitative variables between groups in case of parametric data, while Mann-Whitney test was used in case of non-parametric data. P-value considered statistically significant when $P < 0.05$.

Results

This case- control study includes 80 participants divided into 4 equal groups their demographics data were as follow; the infected cirrhotic group (cirrhotic patients with pharyngitis) were 13(65%) male and 7 (35%) female, the controlcirrhotic group (cirrhotic patients without pharyngitis)13(65%) males and 7 females (35%), their mean age was 59.60 ± 4.32 and 60.25 ± 9.60 respectively. The infected non-cirrhotic group and control non-cirrhotic group include 13(65%) male and 7(35%) female each with their mean age was 44.70 ±9.45 and 56.55 ± 8.80 respectively. The laboratory and radiological demographic data of all groups was shown in (**Table 2, 3**).

In this study the twenty infected cirrhotic patient either were diagnosed clinically to be viral or bacterial their throat swabs reveal organism as follow: 7(35%) patients with Candida, 3 (15%) with gram negative bacilli(15%), 3(15%)Streptococcus and 7(35%) Streptviridans, while in control cirrhotic patients only 5 (25%) their throat swab reveal no growth but the other 15 patient their throat swab reveals the following organisms: 5 (25%) Candidia ,6 (30%)gram negative bacilli including 3(15%)Klebsiella and 3 (15%) providence spp and 4(20%) Staph.Aureus.

Table 2. Demographic laboratory data of cirrhotic patients with acute pharyngitis and cirrhotic patients without pharyngitis

Variables	Cirrhotic patients with pharyngitis (n= 20)	Cirrhotic patients without pharyngitis (n= 20)	p-value
Complete Blood Count (Mean ± SD)			
Haemoglobin **(g/dL)**	9.51 ± 1.83	10.66 ± 1.76	0.050*
Total leucocytes count **($x10^3mm^3$)**	8.84 ± 4.89	6.73 ± 2.61	0.159
Platelets **($10^3/mm^3$)**zz	141.40 ± 56.96	205.90 ± 143.78	0.752
Liver function tests (Mean ± SD)			
AST **(IU/L)**	123.05 ± 71.97	85.95 ± 39.17	0.095
ALT **(IU/L)**	62.75 ± 34.56	56.30 ± 18.66	0.603
Total bilirubin **(mg/dL)**	2.11 ± 0.76	2.09 ± 0.84	0.573
Direct Bilirubin **(mg/dL)**	1.11 ± 0.56	1.25 ± 0.55	0.394
Albumin **(g/dL)**	2.31 ± 0.51	2.10 ± 0.53	0.211
Total protein **(g/dL)**	6.68 ± 1.06	6.99 ± 0.78	0.306
Alkaline Phosphatase **(IU/L)**	170.40 ± 86.08	173.50 ± 80.16	0.387
Renal function tests (Mean ± SD)			
Blood urea **(mg/dL)**	14.29 ± 15.95	7.96 ± 4.24	0.711
Serum Creatinine**(mg/dL)**	1.22 ± 1.04	1.46 ± 0.84	0.199
Coagulation Profile (Mean ± SD)			
INR	1.29 ± 0.19	1.43 ± 0.51	0.264
Abdominal Ultrasound (N %)			
Liver cirrhosis	20 (100%)	20 (100%)	--
Hepatic focal lesion	7 (35.0%)	0 (0%)	0.008*
Splenomegaly	3 (15.0%)	0 (0%)	0.231
Ascites	13 (65.0%)	0 (0%)	0.0001*

AST: Aspartate transaminase, **ALT:** Alanine transaminase, **INR**: International Normalization Ratio, *: statistically significant difference, Independent samples t-test, Fisher Exact test.

Table 3. Demographic laboratory data of non-cirrhotic patients with acute pharyngitis and control non-cirrhotic without pharyngitis

Variables	non-cirrhotic patients with pharyngitis	non-cirrhotic without pharyngitis	p-value
Complete Blood Count (Mean ± SD)			
Hemoglobin**(g/dL)**	11.72 ± 1.55	13.16 ± 2.51	0.035*
Total leucocytes count **($x10^3$ mm^3)**	11.99 ± 4.06	6.15 ± 2.03	0.000*
Platelets **($10^3/mm^3$)**	333.40 ± 43.79	268.45 ± 32.65	0.000*
Liver function tests (Mean ± SD)			
AST **(IU/L)**	45.85 ± 29.67	17.35 ± 2.83	0.000*
ALT **(IU/L)**	33.10 ± 16.37	15.00 ± 5.28	0.000*
Total bilirubin **(mg/dL)**	0.85 ± 0.51	0.35 ± 0.08	0.000*
Direct Bilirubin **(mg/dL)**	0.36 ± 0.26	0.10 ± 0.01	0.013*
Albumin **(g/dL)**	3.21 ± 0.91	3.72 ± 0.45	0.029*
Total protein **(g/dL)**	7.11 ± 0.69	6.97 ± 0.84	0.541
Alkaline Phosphatase **(U/L)**	31.30 ± 6.03	23.05 ± 2.50	0.000*
Renal function tests (Mean ± SD)			
Blood urea **(mg/dL)**	25.55 ± 1.70	28.60 ± 10.69	0.545
Serum Creatinine**(mg/dL)**	1.00 ± 0.17	1.30 ± 0.32	0.003*
Coagulation Profile (Mean ± SD)			
INR	1.14 ± 0.13	1.32 ± 0.22	0.002*

AST: Aspartate transaminase, **ALT:** Alanine transaminase, **INR**: International Normalization Ratio, *: statistically significant difference, Independent samples t-test

The mean ESR level in infected cirrhotic and control cirrhotic were 50.55 ± 36.89 and 38.35 ± 28.69 respectively while the mean CRP level in infected cirrhotic and control cirrhotic were 47.38 ± 9.58 and 53.91 ± 36.37 respectively. With no statistically significant difference in both of them P – value = (0.242) and p- value = (0.684) respectively, (**Table. 4**).

In the non-cirrhotic group the twenty control patient their throat swab reveals no growth while the twenty infected non-cirrhotic patients throat swab reveals the following: ten of them were diagnosed clinically with viral infection with no growth in the swab, while ten patients clinically presented as bacterial infection and their throat swab were as follow 6 (30%) patient streptococcus, 1(5%) Strept.pneumonia, 2(10%) Staph.aureus and 1(5%) H. Influenza. No combined bacterial growth was detected in any of our culture results (in both cirrhotic and non-cirrhotic groups). The mean ESR and CRP levels were significantly higher (P= 0.0001) in the infected non-cirrhotic group (32.35 ± 2.16)(20.35 ± 18.81) than in the control non-cirrhotic group(19.25 ± 10.72) (3.53 ± 3.01) respectively. The mean CRP level in infected non-cirrhotic group and control non-cirrhotic group were 20.35 ± 18.81 and 3.53 ± 3.01 with significant P-value (p-value= 0.0001), (**Table. 5**).

Table 4. CRP, ESR and culture results of cirrhotic patients with pharyngitis and cirrhotic patients without pharyngitis group

Variables	cirrhotic patient with pharyngitis (n= 20)		cirrhotic patient without phayngitis (n= 20)		P-value
	No.	%	No.	%	
ESR: (mm/h)					0.242
Mean ± SD	50.55 ± 36.89		38.35 ± 28.69		
Median (Range)	42.0 (10.0-130.0)		29.1 (5.5-80.0)		
CRP:(mg/dL)					0.684
Mean ± SD	47.38 ± 9.58		53.91 ± 36.37		
Median (Range)	49.5 (27.5-57.5)		48.8 (21.4-129.5)		
Culture:					
Candidiasis	7	35.0%	5	25.0%	0.490
klebsiella	3	15.0%	3	15.0%	1.000
Providence spp.	0	0.0%	3	15.0%	0.231
Staphylococcus aureus	0	0.0%	4	20.0%	0.106
Streptococcal pyogenes	3	15.0%	0	0.0%	0.231
Streptococcal viridans	7	35.0%	0	0.0%	0.008*
No growth	0	0.0%	5	25.0%	0.047*

ESR: Erythrocyte sedimentation rate**, CRP:** C - reactive protein, *: statistically significant difference, Mann-Whitney test, Chi-square test, Fisher Exact test

Table 5. CRP, ESR and culture results of non-cirrhotic patients with pharyngitis and non-cirrhotic patients without pharyngitis group

Variables	non-cirrhotic patient with pharyngitis (n= 20)		non-cirrhotic patient without pharyngitis (n= 20)		P-value
ESR: (mm/h)					0.0001*
Mean ± SD	32.35 ± 2.16		19.25 ± 10.72		
Median (Range)	32.0 (30.0-35.0)		20.0 (6.0-31.0)		
CRP: (mg/dL)					0.0001*
Mean ± SD	20.35 ± 18.81		3.53 ± 3.01		
Median (Range)	12.0 (5.0-48.0)		4.9 (0.0-9.2)		
Culture:					
H.Influenza	1	5.0%	--	--	--
Staphylococcal aureus	2	10.0%	--	--	--
Streptococcal pneumonia	1	5.0%	--	--	--
Streptococcal pyogenes	6	30.0%	--	--	--
No growth	10	50.0%	--	--	--

ESR: Erythrocyte sedimentation rate**, CRP:** C - reactive protein, *: statistically significant difference, Mann-Whitney test

The mean ESR value in viral pharyngitis infected hepatic patients was 50.55 ± 36.89, while in bacterial pharyngitis infected patients it was 38.35 ± 28.69 with no statistically significance difference (p=0.242). The mean CRP value in viral pharyngitis infected cirrhotic patients was 47.38 ± 9.58, while in bacterial pharyngitis infected patients it was 53.91 ± 36.37 with no statistically significance difference (p=0.684), (**Table. 6**).

Table 6. CRP, ESR and culture results of cirrhotic patients with pharyngitis according to presenting clinical manifestations

Examinations	viral pharyngitis (n= 13)		Bacterial pharyngitis (n= 7)		P-value
ESR: (mm/h)					0.242
Mean ± SD	50.55 ± 36.89		38.35 ± 28.69		
Median (Range)	42.0 (10.0-130.0)		29.1 (5.5-80.0)		
CRP: (mg/dL)					0.684
Mean ± SD	47.38 ± 9.58		53.91 ± 36.37		
Median (Range)	49.5 (27.5-57.5)		48.8 (21.4-129.5)		
Culture: (N%)					
Candidiasis	7	53.8%	0	0.0%	0.044*
klebsiella	3	23.1%	0	0.0%	0.521
Streptococcal pyogenes	3	23.1%	0	0.0%	0.521
Streptoccocalviridans	0	0.0%	7	100.0%	0.000*

ESR: Erythrocyte sedimentation rate**, CRP:** C - reactive protein, *: statistically significant difference, Mann-Whitney test, Fisher Exact test

The mean ESR level in the bacterial and viral non-cirrhotic infected patients were 32.35 ± 2.16 and 19.25 ± 10.72 respectively with significant p-value(P=0.0001). The mean CRP value in viral and bacterial non-cirrhotic infected patients were 3.53 ± 3.01 and 20.35 ± 18.81 respectively with significant p-value (P=0.0001), (**Table. 7**).

Table 7. CRP, ESR and culture results of non-cirrhotic patients with pharyngitis according to presenting clinical manifestations

Examinations	Viral pharyngitis (n= 10)		Bacterial pharyngitis (n= 10)		P-value
ESR:(mm/h)					0.0001
Mean ± SD	19.25 ± 10.72		32.35 ± 2.16		
Median (Range)	20.0 (6.0-31.0)		32.0 (30.0-35.0)		
CRP: (mg/dL)					0.0001
Mean ± SD	3.53 ± 3.01		20.35 ± 18.81		
Median (Range)	4.9 (0.0-9.2)		12.0 (5.0-48.0)		
Culture: (N%)					
H.Influenza	0	0.0%	1	10.0%	1.000
Staphylococcal aureus	0	0.0%	2	20.0%	0.474

Streptococcalpneumonia	0	0.0%	1	10.0%	1.000
Streptococcal pyogenes	0	0.0%	6	60.0%	0.011*
No growth	10	100.0%	0	0.0%	0.0001

*: statistically significant difference, Mann-Whitney test, Fisher Exact test

Discussion

An acute inflammation of the pharynx, related to variable pathogen. Infection may be isolated infection of the pharynx and tonsils or part of upper respiratory tract infection **(Perkins, 1997)**; most cases associated with viral common cold (nearly 40% of cases) **(Paradise, 1992)**.

Clinically, it's difficult to distinguish between viral and bacterial pharyngitis clinically especially group A -β-haemolytic streptococci. this overlap in symptoms make clinician tend to give antibiotics for any sore throat, so, pharyngitis is considered a great risk factor for antibiotics resistance and misuse especially in Asia, America, and Europe where a great number of children take antibiotics for treatment of common cold, and upper respiratory tract infections **(Del et al., 2006)**.

Although it's difficult to differentiate different causes of pharyngitis clinically, but some micro-organisms give special manifestations that give clues to clinical suspicion.

Chronic liver disease patients, including those with cirrhotic, are particularly susceptible to infections as the immune system is dysfunctional through several pathological mechanisms including decreased opsonization, reticuloendothelial dysfunction, neutrophils impairment and abnormal immunoglobulin synthesis **(Wiest et al., 2014 ; Stroffolini et al., 2021)**. It's known that gram negative bacteria is difficult to be isolated from the throat swab, however, cirrhotic patients are liable to nosocomial infection which could be gram negative isolate (klebsiella pneumonia, Pseudomonas, etc). **(Lagadinou and Gogos, 2015)**.

Many studies have been done to differentiate bacterial and viral infection with the use of acute phase reactants such as CRP, ESR, 2-5-oligoadenylate synthetase, etc **(Somro et al., 2011)**.

In this study CRP and ESR in cirrhotic patient are statistically non-significant in both infected cirrhotic either viral or bacterial and in control cirrhotic patients, while in non-cirrhotic group they were statistically significant values between infected and control patient and between the viral and bacterial pharyngitis in non-cirrhotic infected patients; and this agree with Somro et al. In their study on CRP as acute phase reactant protein in acute tonsillitis; the throat swab in patients with bacterial growth was about four times CRP positive results in comprising to those with no growth. **(Somro et al., 2011)**.

Similar reports were observed by many studies involve acute tonsillitis in their study, but disagree with **Bakashi and Chatterji** who concluded that C reactive protein can't differentiate between viral and bacterial pharyngitis. Led to the conclusion

that the measurement of acute phase reactants cannot differentiate between viral or bacterial tonsillitis **(Stjernquist-Desatnik et al. 1987) (Ylikoski and Karjalainen, 1989; Bakashi and Chatterji, 2008; Kaya et al., 2014)**.

Concerning with throat culture in hepatic patient, our study reveal that **75%** of non-complaining patient reveal growth. The cirrhotic patients who diagnosed clinically as viral pharyngitis their culture growths were 53.8%Candida, 23%gram negative bacilli and 23% were Streptococcal pyogenes. The cirrhotic patients who diagnosed clinically as bacterial pharyngitis reveal Strept.Viridans growth in their culture and it is known that, Streptococcal Viridans bacteria normally inhabit the mucosa of oral cavity, digestive system and urinary system. In immunocompetent persons Strept.Viridans bacteria have low pathogenic liability. However, in certain patient populations, Veridans group Streptococci **(VGS)** can cause invasive disease, such as endocarditis, intra-abdominal infection, and shock **(Doern and Burnham, 2010)**.

In our study the cirrhotic patients being immunocompromised patients explain flaring of this low pathogenic organism inducing infection and must kept in mind that Within the VGS, the rates and patterns of antimicrobial resistance vary greatly depending upon the species identification and the patient population

Conclusion

In immune-compromised patient complaining sore throat must undergo complete history clinical examination and throat culture to identify the organism and apply the most appreciated treatment either antifungal or bacterial to avoid antibiotic abuse, misuse and bacterial resistance.

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