

Original Article

# Inflammatory Response and Hepatic Injury Markers in Children and Adult Patients Infected with Influenza Virus: A Hospital-Based Cross-Sectional Study

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## Abstract

**Background and Aim:** Influenza mainly involves the pulmonary system, but may cause damage to other organs like liver, kidneys, and bone marrow. It is essential to identify changes in the laboratory markers indicating inflammation and hepatic injury; and changes in white blood cell count in patients with flu. This study aimed to evaluate these laboratory markers and compare them in children and adults.

**Methods:** This retrospective study was performed in three university hospitals in Qazvin, Iran. Clinically available laboratory biomarkers including some inflammatory markers (e.g. CRP and ESR), marker of hepatic injury (AST, ALT, ALP, bilirubin, prothrombin time), and white blood cell count of 435 definite influenza patients with positive influenza RT-PCR in 2018 and 2019 were collected from their medical records. The results were classified based on age (over 14 years of age in adults) and the normal range reported by the performing laboratory. Using SPSS software 25, data were analyzed by chi-square and Pearson correlation coefficient test.  $P < 0.05$  was considered significant.

**Results:** Leukocytosis was observed in 22.5% of adults and 1.0% of children, and the difference between the two groups was significant ( $p < 0.001$ ). ESR was increased in 91.6% of children and 86.9% of adults; CRP was elevated in 34.7% of adults while 80.5% of children showed elevation ( $p < 0.001$ ). The duration of hospital stay was significantly correlated with ESR ( $p < 0.001$ ,  $r = 0.177$ ), and CRP ( $p = 0.002$ ,  $r = 0.163$ ). The increase in ALT was detected in 32.1% of adults versus 10.0% of children and AST in 38.6% of adults versus 10.0% of children. This increase in both liver enzymes was greater in adults compared with children ( $p < 0.044$  and  $p < 0.013$ , respectively). 42.4% of adults, showed increased prothrombin time.

**Conclusion:** Leukocytosis, CRP elevation and increase in liver enzymes during influenza seems to be more pronounced in adults than in children. The results also showed a significant relationship between a hospital stay and the level of ESR and CRP.

**Keywords:** Influenza; Liver Function Tests; Biomarkers; Blood Sedimentation; C-Reactive Protein.

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## Introduction

Infectious diseases are the cause of about one-third of all deaths worldwide (1). Influenza as an acute respiratory infection annually carries a significant burden of respiratory infection (about 2%) and deaths worldwide (2-4). Among influenza virus types, types A (H1N1, H3N2) and B can cause seasonal outbreaks of the disease (5). Influenza is classified as a negative-sense RNA virus belonging to the Orthomyxoviridae family (6). Although mild symptoms of respiratory

infection are found in non-severe cases, the most prominent clinical manifestations of influenza are atypical acute pneumonia and lung injury, which can lead to multiple organ failure and ultimately lead to death, especially in patients with multiple underlying diseases (7). Definite diagnostic tests for this disease include serological and molecular tests, including Real Time-Polymerase Chain Reaction (RT-PCR), which indicate whether it is positive or negative and the types of virus subtypes (8, 9). Before the COVID-19 pandemic, the influenza virus was considered to be the

main cause of respiratory infections worldwide. However, its pathogenesis is not fully understood. Influenza, in addition to the respiratory system, can negatively affect the function of other vital organs such as the liver, kidneys, cardiovascular system, and central nervous system (10-15). The mechanism of influenza-related liver damage is not yet fully understood and is still controversial. There is evidence to support the hypothesis that the influenza virus can affect other parts of the body in addition to the lungs due to the immune response to viral antigens (16). Alanine amino-transaminase (ALT), aspartate amino-transaminase (AST), alkaline phosphatase (ALK), total bilirubin, and direct bilirubin are considered liver damage screening tests (17). Abnormal liver function can be determined by examining albumin levels and coagulation tests, including prothrombin time (PT) (18). Some reports suggest that patients with influenza have elevated serum levels of liver enzymes and varying degrees of damage to liver tissue (19, 20). In this study, we assessed the characteristics of hepatic, renal, and inflammatory function markers and their changes in patients with influenza, identified the prevalence of abnormal levels of biomarkers, found correlations with other biomarkers, and compared them in pediatric and adult populations. It makes the mechanism of pathogenesis of the virus better known.

In this clinical study, we examined the changes in these biomarkers in hospitalized patients with seasonal influenza. Also, in the literature, there are a limited number of studies on the comparison of children and adults regarding this subject. Therefore, we aimed to investigate the similarities and differences between biomarkers of adults and children with seasonal influenza.

## Methods

**Study design:** This retrospective study was performed cross-sectionally based on the information in the medical records of patients with influenza in 2018 and 2019 in three teaching hospitals at Qazvin University of Medical Sciences (Qods, Bou- Ali Sina, and Velayat). This study was approved by the Ethics Committee of Qazvin Medical Sciences. All data were anonymized to ensure privacy and confidentiality of patients' personal information, with each participant assigned a unique identifier.

For this purpose, the medical records of hospitalized patients and positive influenza RT- PCR results from

the Qazvin provincial reference laboratory were carefully reviewed. If the file was incomplete, a resume was taken from those around the patient. The variables studied in this study included age, sex, and length of hospital stay. In addition to demographic information, typing and subtyping of influenza viruses [types A (H1N1, H3N2) and B], laboratory biomarkers of patients including hematologic biomarker Wight Blood Cells (WBC), serum sodium and potassium levels, biochemical markers (ALT, AST, D Bill, T Bill, and albumin), inflammatory markers: Erythrocyte Sedimentation Rate (ESR) and C- Reactive Protein (CRP) and coagulation markers prothrombin time (PT), International Normalized Ratio (INR) were also examined. The results were classified based on age (over 14 years of age in adults) and the normal range reported by the performing laboratory. Based on age and data of 435 cases, patients were extracted from medical records. All patients with positive RT- PCR, regardless of age, ethnicity, and gender restrictions were included in the study. Patients with recent chemotherapy, a history of the hepatobiliary disease, and incomplete information were excluded.

**Statistical analysis:** The collected data were presented using frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables. Considering that many common lab tests including complete blood count and blood biochemistry have different normal values between children and adults, mean comparison tests were not applicable to compare the numerical average of the laboratory markers between the two groups. Therefore, the results were classified based on the normal range reported by the performing laboratory and expressed as frequency and percentages and comparisons among groups were carried out using chi-square test. To investigate the relationship between qualitative and quantitative variables (age and length of hospital stays [LOS]), Pearson correlation coefficient was used. All statistical analyzes were performed using SPSS software version 25. P-value <0.05 was considered a significant level.

## Results

Of the total number of hospitalized patients (435 cases), 206 were men (33% children, 67% adults) and 229 were women (14.8% children, 85.2% adults). most patients (75.6%) were infected with type A virus, including (H1N1, and H3N2). Table 1 are shown the

results of laboratory examinations. As shown in Table 1, ESR has been increased in 87 (91.6%) children and 265 (86.9%) adults. CRP has been increased in 33 children (34.7%) and 215 adult (80.5%) patients with influenza. The rate of increase in adults was significantly higher than in children ( $p < 0.001$ ). The

increase in alanine aminotransferase observed in 32.1% of adults versus 10.0% of children and increase in alanine aspartate aminotransferase was found in 38.6% of adults versus 10.0% of children. In fact, increase of ALT and AST levels in adults was significantly higher than in children. ( $p < 0.044$  and  $p < 0.013$ , respectively).

**Table 1.** Laboratory examination (the inflammatory, and hepatic injury markers) of children and adult hospitalized patients with influenza in Qazvin Province during 2018–2019.

Variables		Children		Adult		Total		P-value
		n	(%)	n	(%)	n	(%)	
Gender	Male	68	(66.7)	138	(41.4)	206	(47.4)	< 0.001*
	Female	34	(33.3)	195	(58.6)	229	(52.6)	
Year	2018	47	(46.1)	190	(57.1)	237	(54.5)	0.051
	2019	55	(53.9)	143	(42.9)	198	(45.5)	
Erythrocyte Sedimentation Rate (ESR)	Normal	8	(8.4)	40	(13.1)	48	(12.0)	0.219
	Increased	87	(91.6)	265	(86.9)	352	(88.0)	
C-Reactive protein	Normal	62	(65.3)	52	(19.5)	114	(31.5)	< 0.001*
	Increased	33	(34.7)	215	(80.5)	248	(68.5)	
Sodium (Na)	Hypernatremia	0	(0)	1	(0.3)	1	(0.2)	0.320
	Normal	73	(75.3)	264	(81.5)	337	(80.0)	
	Hyponatremia	24	(24.7)	59	(18.2)	83	(19.7)	
Potassium (K)	Hyperkalemia	5	(5.3)	11	(3.4)	16	(3.8)	0.583
	Normal	82	(86.3)	279	(85.8)	361	(86.0)	
	Hypokalemia	8	(8.4)	35	(10.8)	43	(10.2)	
Aspartate aminotransferase (AST)	Increased	2	(10.0)	44	(38.6)	46	(34.3)	0.013*
	Normal	18	(90.0)	70	(61.4)	88	(65.7)	
Alanine aminotransferase (ALT)	Increased	2	(10.0)	36	(32.1)	38	(28.8)	0.044*
	Normal	18	(90.0)	76	(67.9)	94	(71.2)	
Alkaline phosphatase (ALP)	Increased	0	(0)	9	(8.5)	9	(7.8)	0.363
	Normal	9	(100)	97	(91.5)	106	(92.2)	
Albumin	Normal	1	(50.0)	11	(64.7)	12	(63.2)	0.683
	Hypoalbuminemia	1	(50.0)	6	(35.3)	7	(36.8)	
International normalized ratio (INR)	Increased	2	(28.6)	76	(37.4)	78	(37.1)	0.633
	Normal	5	(71.4)	127	(62.6)	132	(62.9)	
Prothrombin time (PT)	Increased	2	(28.6)	87	(42.4)	89	(42.0)	0.465
	Normal	5	(71.4)	118	(57.6)	123	(58.0)	
Direct bilirubin	Increased	0	(0)	29	(30.9)	29	(30.2)	0.347
	Normal	2	(100)	65	(69.1)	67	(69.8)	
Total Bilirubin	Increased	0	(0)	23	(24.5)	23	(24.0)	0.422
	Normal	2	(100)	71	(75.5)	73	(76.0)	
White blood cell	Leukocytosis	1	(1.0)	75	(22.5)	76	(17.5)	< 0.001*
	Normal	87	(85.3)	223	(67.0)	310	(71.3)	
	Leukopenia	14	(13.7)	35	(10.5)	49	(11.3)	
Type of virus	A	84	(82.4)	245	(73.6)	329	(75.6)	0.071
	B	18	(17.6)	88	(26.4)	106	(24.4)	

Leukocytosis was observed in 22.5% of adults and 0.1% of children, which was a significant difference between the two groups ( $p < 0.001$ ). In the adult group, in 42.4% of cases, these coagulation tests were impaired. However, due to the small number of PT and INR tests performed in children, changes in these markers in this subgroup could not be studied. The

relationship between biomarkers and age and LOS in a hospitalized patient with seasonal influenza can be seen in Table 2. In examining the correlation between demographic and clinical variables with laboratory parameters, length of hospital stay with ESR ( $p < 0.001$ ,  $r = 0.177$ ), and CRP ( $p = 0.002$ ,  $r = 0.163$ ) had a significant relationship.

**Table 2.** Relationship between laboratory markers and age and length of hospital stay in hospitalized patients with seasonal influenza.

Variable		ESR	CRP	AST	ALT	ALP	Billi-D	Billi-T	WBC
Age	Correlation	0.189**	0.368**	0.094	0.082	- 0.328**	0.127	0.202*	- 0.066
	P	< 0.001	< 0.001	0.278	0.350	< 0.001	0.217	0.049	0.171
LOS	Correlation	0.177**	0.163**	- 0.039	- 0.065	- 0.027	0.043	0.069	0.080
	P	< 0.001	0.002	0.657	0.462	0.775	0.682	0.508	0.095

ESR: Erythrocyte sedimentation rate; CRP: C Reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Billi-D: Direct bilirubin; Billi-T: Total bilirubin; WBC: White blood cell; LOS: Length of hospital stays

## Discussion

In our study, male children were the most affected group. Greater biological susceptibility to more severe manifestation and more health care-seeking / access of male children (surveillance/detection bias) are two probable main reasons for the sex difference in hospitalization. In hospitalized patients with influenza, clinical attention is focused on respiratory tract involvement, so the clinical significance of liver involvement is unclear. To the best of our knowledge, this is the first report comparing liver involvement in pediatric and adult patients with influenza. Although the laboratory characteristics of patients with influenza have been studied in some reports (10, 17, 21-25) in none of the studies, children, and adult patients with influenza have been compared according to inflammatory biomarkers (ESR and CRP), hematological biomarkers (WBC), serum sodium and potassium, some biochemical markers (ALT, AST, ALP, D Bill, and T Bill and albumin) and coagulation markers (PT, INR). Identifying appropriate biomarkers and finding links to other biomarkers will help to better identify the pathogenicity of the virus.

In this study, elevated CRP levels were significantly different between children and adults. The elevated CRP did show in 34.7% of children and 80.5% of adults. While, the inflammatory marker ESR increased in 91.6% of children and 86.9% of adults, respectively. At the time of hospital admission, the raised ESR seems to be a more sensitive indicator than CRP in children

(raised ESR in 91.6% vs. raised CRP in 34.7%). The raised ESR in our study (80.9%) was more prevalent than in the study of Huang et al. and conversely, raised CRP in the study of Huang et al. was more frequent than in our study (12). In this study, there is a significant direct correlation between the length of hospital stay and inflammatory markers (both ESR and CRP) in patients with influenza. In the study of Merakoulis et al., a slight increase in CRP was shown (21). Siddiqui et al. (26) and Melbye et al. (27) confirmed a raised CRP and ESR in patients with influenza, regardless of age in both studies. CRP is a nonspecific biomarker of acute inflammation that is produced in the liver as a response to factors released by macrophages and adipocytes (28). Some researchers have reported that increased CRP is a clinical feature observed in most patients with influenza and COVID-19 infection (27, 29). In our study, a significantly raised CRP level was also observed in the adult patients; about 80% of hospitalized adults and only 35% of children had increased CRP. Influenza in adults may cause a more severe Systemic Inflammatory Response Syndrome (SIRS) than influenza in children. The reason may be related to the immature immune system of the children, which will not cause an excessive response. Other possible effects on the relationship between age and CRP concentrations are smoking and obesity. It has been shown that CRP levels are affected by smoking (possibly through inflammatory and tissue-damaging effects). Obesity is also associated with increased CRP

concentrations (probably because adipose tissue is an important site for the production of interleukin-6, a major regulator of CRP gene expression) (30).

Although hospitalization time was limited due to the hospital's capacity during the influenza outbreak, a correlation was still evident between the length of hospital stay and the results of CRP and ESR inflammatory tests.

ALT levels increased in 10.0% of children and 32.1% of adults and AST levels increased in 10.0% of children and 38.6% of adults respectively, a statistically significant difference was observed between the two groups. In the study of Huang et al., an increase in ALT and AST was found (12). In Yang et al.'s study, an increase in ALT of 80.93% and AST in 56.13% of cases of influenza were reported, which was higher than the incidence rates in our study. In this study, the distribution of age diversity was not considered, but in our study, by classifying individuals as adults and children, the differences in changes were carefully examined. In our study, an increase in liver enzymes was observed in both children and adults, although these changes were more common in adults. In our study, ALT and AST were all performed before the application of antiviral therapy. Thus, the increase in AST is not likely to be induced by the drug. This may, to some extent, indicate that adults with Influenza infection are more prone to liver cell damage. However, due to the small sample size of this study and the lack of literature reports on liver function impairments in children and adults, we cannot yet make a definite conclusion. Zarogoulidis et al. and Soleimani et al. also reported abnormal levels of liver enzymes in patients with H1N1 positive and hepatic impairment (10, 19). Elevated liver transaminase levels are a frequent observation during a number of systemic infections (31). However, the extent of liver damage in influenza has not been determined and the pathogenesis of liver involvement is not yet well understood. Severe progression of the flu may cause tissue perfusion disorders that eventually contribute to liver cell damage and elevated liver transaminase levels. However, no specific feature of ischemic hepatitis was found in any of our patients. All patients had mild and transient liver lesions.

Our study presents interesting findings from liver involvement during influenza infection. First, serum AST and ALT levels were significantly higher in the adult group than in children. Second, the length of hospital stay seems to be related to abnormalities in

liver serum enzymes and age, and liver damage is more prevalent in older ages (20). Bermejo-Martin et al observed higher levels of proinflammatory cytokines in adult influenza (32). In addition, the influenza virus can cause a cytokine storm that can directly damage the liver during a flu infection and should be considered a hepatotropic virus (19).

Analyzing biochemical and inflammatory markers showed that there is no significant relationship between these variables (the increase in AST, ALT, ALP, Bili D, Bili T, and the increase in inflammatory markers) in patients with influenza. Similarly, in the study by Soleimani et al., they reported a significant increase in liver enzymes (ALT, AST) and no change in Bili D and Bili T in patients with influenza (10). While our study showed an increase in AST and ALT in both groups and an increase in bilirubin only in the adult group. In our study, the level of ALP was also examined and its increase was observed only in a small percentage of the adult age group. The higher prevalence of underlying bile duct abnormality in adults than in children may be the reason for this finding. In Papic et al.'s study, raised ALT, ALP, and Bili T in pandemic and seasonal flu and raised AST in 48.66% and raised CRP in 56% of seasonal flu and 76.18% in pandemic influenza have been reported (11). In our study, an increase in ALT and AST was observed in both age groups. In another study by Premkumar et al. and Yükselmiş et al., the levels of both liver enzymes (ALT and AST) were significantly increased, but in contrast to our study, which reported an increase in Direct and total Bilirubin, their levels in the study of Premkumar et al., were in the normal range (22).

An analysis of hematological markers showed a significant difference in WBC count between adults and children. In the present study, leukocytosis was observed in 22.5% of adults and only in 0.1% of children. In the study of Huang et al., an increase in WBC count was found in patients with influenza (12). Soleimani et al. reported an increase in PT of 14.97% of influenza cases (10). In our adult group, about 40% of these coagulation tests were transiently impaired. However, due to the small number of PT and INR tests performed in children, changes in these markers in this subgroup could not be interpreted. In another study by Premkumar et al., The INR was normal in adult cirrhotic cases of influenza (22).

The main limitation of this study is the retrospective collection of information. According to the results of the current research, it is suggested that research be

conducted with a higher sample size in different regions of the world. Also, further basic studies are needed to better understand the pathophysiology of liver involvement in influenza.

## Conclusion

Leukocytosis, CRP, and increase in liver enzymes during influenza seem to be more pronounced in adults than in children. The results also showed a significant relationship between the duration of hospitalization and the level of CRP and ESR.

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## Conflict of Interest

The authors declared that they have no conflict of interest associated with this study.

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## Ethics

This study was conducted in accordance with the research priorities of Qazvin University of Medical Sciences and was approved by the ethics committee of the university.

Code of Ethics: IR.QUMS.REC.1397.180

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