ELEVATED SERUM AMYLOID A LEVEL PREDICTS SEVERITY OF RADIOLOGICAL LUNG INVOLVEMENT IN HOSPITALIZED CHILDREN WITH COVID-19

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ABSTRACT:

Background: *Several biomarkers were studied in COVID-19 for risk stratification and monitoring disease progression.*

Aim of the work: *We aimed to investigate the dynamics of serum amyloid A in children hospitalized with confirmed SARS-CoV-2 infection. Also, correlations with clinical presentation, disease severity score, radiological lung involvement, and outcome were studied.*

Patients and Methods: *This controlled cross-sectional study included 60 participants divided into 2 equal groups of patients and controls. Thirty children with confirmed COVID-19 diagnosis were recruited from the Pediatric department, Children's Hospital, Ain Shams University, from October 2020 to March 2021. Thirty age and sex-matched healthy children served as controls. Amyloid A was estimated in serum on admission (Day 1) and 10 days after treatment using ELISA method. Chest computed tomography was performed for all patients on admission.*

Results: *At presentation, serum amyloid A was significantly higher in patients (median (IQR)= 420 (300-600)) compared to controls (median (IQR)= 50 (40-70)) ($p<0.001$). A cut-off value> 100 ug/ml discriminated patients from controls with 100 % sensitivity and specificity, area under the curve =1, $p<0.0001$. Serum amyloid A was significantly higher in patients with respiratory distress ($p=0$), hypoxia ($p=0.003$), hypotension ($p=0.02$), and abnormal radiological findings ($p=0.03$). Comparing COVID-19 severity grades, serum amyloid A was significantly higher among severe and critically ill patients ($p=0.001$). Serum amyloid A positively correlated with the number of affected lung lobes ($r=0.46$, $p=0.01$) and radiological severity score 9$r=0.51$, $p=0.004$). Follow-up serum amyloid A level significantly declined compared to day 1 ($p=0.001$). However, non-survivors showed a significant increase in serum amyloid A level (median (IQR)= 930 (840-1020)) ($p=0.01$).*

Conclusions: *Serum amyloid A is a useful biomarker for severity and prognosis in children with COVID-19. Also, it can reflect severity of radiological lung involvement.*

Keywords:

Serum amyloid A, COVID-19 in children, SARS-CoV-2 infection

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the world health organization (WHO) in March 2020 and is still ongoing.[1] The culprit organism is the severe acute respiratory syndrome

coronavirus-2 (SARS-CoV-2) that principally targets the human respiratory tract causing a spectrum of manifestations varying from upper airway involvement to life-threatening acute respiratory distress syndrome (ARDS).[3] In children, multisystem inflammatory syndrome (MIS-C) was described in severe cases.[4] Although reverse transcription polymerase chain reaction (RT-PCR) is required to confirm COVID-19 diagnosis, chest computed tomography (CT) was widely used as a supporting tool, especially in patients with moderate to severe disease and risks for disease progression.[5] Factors correlated with COVID-19 disease progression have been described.[5] Additionally, several biomarkers have been utilized for risk stratification regarding COVID-19 disease severity and prognosis.[6]

Serum amyloid A (SAA) is an acute-phase protein released by hepatocytes in response to inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6).[7] Exponential up-regulation occurs as a part of the inflammatory cascade when Toll-like receptors on innate immune cells recognize pathogen-associated molecular patterns.[8] SAA has been identified in serum of individuals with acute on top respiratory conditions.[9] Also, it was found to be more sensitive than C-reactive protein (CRP) in detecting minor inflammatory stimuli.[10] Persistent elevation can reflect ongoing inflammation.[11] Its clinical value has gained attention during the COVID-19 pandemic. Several studies have confirmed its role as a valuable biomarker in identifying severity and prognosis in adult patients infected with SARS-CoV-2.[12,13] However, in children, the results were inconclusive.

AIM OF THE WORK:

This work aimed to investigate the dynamics of serum amyloid A in children hospitalized with confirmed SARS-CoV-2 infection. Also, correlations with clinical presentation, disease severity score, radiological lung involvement, and outcome were studied.

PATIENTS AND METHODS:

This controlled cross-sectional study included a total of 30 children hospitalized with confirmed COVID-19 infection that were recruited from the Pediatric Department, Children's Hospital, Ain Shams University, Cairo, Egypt, during the period from October 2020 to March 2021. They were subdivided into 16 patients with respiratory distress and 14 patients without respiratory distress. The control group comprised 30 age and sex-matched healthy children. They had no history of contact with a suspected or confirmed case of COVID-19 infection.

Informed consent was obtained from parents or guardians before participation. This study was performed in line with the Helsinki Declaration of 1975. Approval was granted by the Research Ethics Committee of human experimentation, Faculty of Medicine, Ain Shams University (FMASU MS 744/2020).

Nasopharyngeal and throat swabs were collected from all enrolled patients on admission, and SARS-CoV-2 RNA was detected using reverse transcription-quantitative polymerase chain reaction (PCR). Patients with associated chronic inflammatory conditions or infections that elevate serum amyloid A were excluded.

A detailed history was obtained from all patients and controls, including demographic data, clinical symptoms, comorbidities, and infected contact. A thorough clinical examination was performed with special emphasis on vital data. Oxygen saturation (SPo2) was measured using pulse oximetry, and hypoxia was defined as SPo2 ≤ 92%. Also, patients were graded into 4 categories

of COVID-19 disease severity according to WHO Interim Guidance, 2020: mild, moderate, severe, and critically ill.[14]

Initial laboratory results on admission (Day 1) were collected from the patient's records, including differential blood counts, liver and kidney functions, and inflammatory parameters (CRP, ESR, LDH, ferritin, and D-dimer).

Laboratory work-up:

Venous blood samples (2-3 ml) were collected under aseptic conditions from all patients and controls on day 1 (before treatment) and 10 days after treatment, centrifuged at 2000-3000 rpm for 20 minutes, and stored at -20ºC for further use. Serum amyloid A level (ug/ml) was measured using a commercially available ELISA kit supplied by Bioassay Technology Laboratory (Shanghai, China) according to manufacturer instructions.

Radiological assessment:

Upon enrollment, all patients underwent chest computed tomography (CT) using a 32-slice CT machine (Optima CT, GE "General Electric", USA). The CT images were interpreted by an experienced radiologist for the number of affected lobes, type, laterality, and distribution of abnormalities. Each of the 5 lung lobes was given a score from 0 (none) to 4 (severe) according to the degree of radiological involvement then a total radiological severity score was calculated by summation of all 5 lobes scores.[15]

Statistical analysis:

Data were analyzed using Statistical Package for social science, version 23.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data with parametric distribution were presented as mean, standard deviation (SD), and ranges, while non-parametric were presented as median with inter-quartile range (IQR). Categorical variables were presented as numbers (n) and percentages (%). Chi-square test was used for comparison between 2 groups regarding qualitative variables. For comparison between 2 groups with quantitative variables, Independent t-test (parametric) and Mann-Whitney test (non-parametric) were used. A one-way analysis of variance (ANOVA) for parametric data and Kruskal-Wallis test for non-parametric data were used to compare more than 2 independent groups with quantitative variables. Spearman correlation coefficients were used to assess correlation between 2 quantitative parameters in the same group. Receiver operating characteristic curve (ROC) was used to assess cut-off point with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve (AUC). Confidence interval was set at 95%, and margin of error accepted was set to 5%. So, P-value was considered significant if <0.05.

Ethical approval and consent to participate:

This study was performed in line with principles of the Declaration of Helsinki 1975. Approval was granted by Research Ethics Committee of human experimentation of Ain shams university (FMASU MS 744/2020). Informed consent was obtained from a parent and/or legal guardian of all participants before enrollment.

RESULTS:

Thirty children with confirmed COVID-19 infection included 10 males (33.3%) and 20 females (66.6%). Their age ranged from 2 months to 16 years, with a median (IQR) of 6 (1.25 - 9.17) years. The mean ±SD duration of admission was 13.73 ±5.25 days. 20% had associated co-morbidities. They were graded according to the COVID-19 disease severity index into 13 mild (43.3%), 7 moderate (23.3%), 3 severe (10%), and 7 critically ill (23.3%) cases. Mortality was the outcome in 2 (6.7%) cases.

For comparing serum amyloid A levels, SARS-CoV-2 positive patients were well matched with controls with a mean age of 4.34 (1 - 8) years regarding age (p=0.42) and sex (p=0.59). serum amyloid A level was significantly higher among patients on day 1 (median (IQR)= 420 (300-600)) and day 10 (median (IQR) = 260 (200-300)) compared to controls (median (IQR)= 50 (40-70)) (p<0.001, p=0 respectively) (Figure 1)

Table 1 shows clinical symptoms and signs frequency in infected children with SARS-coV-2. The most frequent symptom was fever in 100% of patients, with a mean ±SD body temperature of 38.4 ±0.58ºC followed by abdominal pain (60%), dyspnea (53.3%), and cough (50%). Hypoxia was elicited in 33.3% with mean ±SD SPo2 of 92.13 ±4.67%. The mean ±SD systolic and diastolic blood pressures were 92.7 ±20.75 and 61.4 ±12.79 mmHg, respectively. Hypotension was present in 30% of cases.

Radiological CT abnormalities were detected in 22 (73.3%) patients. The median (IQR) number of lobes affected was 2 (0-4). Distribution was bilateral in 56.7%, posterior in 63.3%, and peripheral in 40% of cases. The most common radiological finding was ground glass opacities (66.7%), followed by subpleural lines (63.3%) and consolidation (53.3%). (Table 1)

As shown in Table 2, there was no significant difference between patients with and without respiratory distress regarding routine acute phase reactants collected on day 1: CRP (p=0.23), ESR (p=0.75), LDH (p=0.24), and ferritin (p=0.08). D-dimer was significantly higher in patients with respiratory distress (p=0.01). Also, there was no significant difference between COVID-19 disease severity grades regarding CRP and ESR (p= 0.05, 0.7). D-dimer, ferritin, and LDH were significantly higher in critically ill cases (p=0.003, 0.002, 0.04). (Table 3)

The median (IQR) total radiological severity score was significantly higher in patients with respiratory distress 8.5 (4.5-11) and in severe 9 (9-11) and critically ill 11(6-12) cases. (Table 2&3)

Serum amyloid A measured on day 1 was significantly higher in patients with respiratory distress (median (IQR)=580 (460-600)) compared to those with no respiratory distress (median (IQR)=310 (285-360)) (p=0). Also, it was significantly higher among those with severe COVID-19 disease median (IQR)= 600 (600-610) compared to mild and moderate cases (p=0.001). (Table 2&3)

Furthermore, patients presented with hypoxia and hypotension showed significantly higher levels of serum amyloid A on day 1 (P=0.003, 0.02, respectively) (Table 4).

As shown in Table 4, patients with chest CT abnormalities were associated with a significantly higher level of serum amyloid A median (IQR)= 500 (300-600) compared to those with undetected radiological findings median (IQR)= 345 (292.2-372.5) (p=0.03).

Serum amyloid A concentration measured on day 1 was negatively correlated with oxygen saturation (r=-0.56, p=0.001), systolic and diastolic blood pressures (r=-0.55, p=0.001). Also, it was positively correlated with the total radiological severity score (r=0.51, p=0.004) and number of affected lung lobes (r=0.46, p=0.01). There was no significant correlation between serum amyloid A and inflammatory parameters collected at presentation. (Table 5)

There was a significant decline in serum amyloid A level on day 10 after treatment (median (IQR)= 260 (200-300)) compared to that at presentation (p=0.001). (Figure 2). However, non-survivors showed sustained elevation in serum amyloid A levels median (IQR)= 930 (840-1020), and it was

significantly higher compared to survivors (median (IQR)=250 (190-295)) when measured on day 10. (Table 6)

A cut-off value of serum amyloid A of >400 ug/ml was able to discriminate COVID-19 patients with chest CT abnormalities with 87.5% sensitivity, 93.3% positive predictive value, 92.8% specificity, 86.7% negative predictive value, and area under the curve (AUC)=0.86, p<0.0001. (Figure 3)

Table 1: Demographic, clinical and radiological characteristics of the studied patients

	N=30
Age (years), Median (IQR)	6 (1.25 – 9.17)
Sex (M / F), n (%)	10 /20 (33.3% / 66.7%)
Symptoms & Signs	n (%)
Fever	30 (100.0%)
Cough	15 (50.0%)
Dyspnea	16 (53.3%)
Loss of smell	1 (3.3%)
Loss Of Taste	1 (3.3%)
Diarrhea	6 (20.0%)
Nausea	15 (50.0%)
Vomiting	13 (43.3%)
Fatigue	14 (46.7%)
Headache	3 (10.0%)
Rash	9 (30.0%)
Conjunctivitis	5 (16.7%)
Abdominal pain	18 (60.0%)
Muscle ache	11 (36.7%)
Sore throat	9 (30.0%)
Runny nose	7 (23.3%)
Hypoxia	10 (33.3%)
Hypotension	9 (30.0%)
Respiratory distress	16 (53.3%)
Temperature (˚C), mean ± SD	38.48 ± 0.58
Heart rate (beat/minute), mean ± SD	117.33 ± 24.10
Oxygen saturation (%), mean ± SD	92.13 ± 4.67
Systolic Blood pressure (mmHg), mean ± SD	92.70 ± 20.75
Diastolic Blood pressure (mmHg), mean ± SD	61.40 ± 12.79
CT-chest abnormalities (n=22)	
Number of affected lobes, median (IQR)	2 (0 – 4)
Type of lesion	
Ground Glass Opacities, n (%) Sub pleural lines, n (%) Consolidation, n (%)	20 (66.7%) 19 (63.3%) 16 (53.3%)
Distribution	
Unilateral, n (%) Bilateral, n (%) Posterior, n (%) Antero- Posterior, n (%) Central, n (%) Peripheral, n (%) Central-peripheral, n (%)	5 (16.7%) 17 (56.7%) 19 (63.3%) 3 (10.0%) 2 (6.7%) 12 (40.0%) 8 (26.7%)

Table 2: Comparison between clinical severity grades regarding laboratory data and radiological parameters in studied patients.

		All patients	COVID-19 Clinical severity index				Test value	P-value
			Mild	Moderate	Severe	Critically ill		
		No.=30	No. = 13	No. = 7	No. = 3	No. = 7		
TLC ($x10^3$/u L)	Mean ± SD	12.58 ± 7.03	12.66±6.76	12.10±7.34	12.27±8.08	13.06±8.44	0.022•	0.996
	Range	3 – 23	3.7–23	4.5–22.4	3–17.8	3–23		
Absolute lymphocytic count ($x10^3$/u L)	Median (IQR)	2.3 (1.9 – 3)	2.8(2 – 4.43)	1.9(1.6 – 3)	2.62(1.3 – 2.8)	2(2 – 2.5)	3.574≠	0.311
	Range	0.4 – 6.7	0.4–6.7	0.6–5.8	1.3–2.8	0.9–3		
Absolute neutrophilic count ($x10^3$/u L)	Median (IQR)	6.7 (4 – 14.4)	5.71(4 – 14)	6(4.8 – 13.4)	8(0.17 – 14.4)	8(1.9 – 17)	0.405≠	0.939
	Range	0.17 – 19	1–18	2.3–14.6	0.17–14.4	1.7–19		
Hemoglobin (g/dl)	Mean ± SD	9.92 ± 1.64	9.48±1.97	10.31±1.62	10.73±0.70	9.99±1.24	0.667•	0.580
	Range	4.9 – 12.8	4.9–11.5	7.6–12.8	10–11.4	9–12.6		
Platelets ($x10^3$ /u L)	Median (IQR)	308.5 (188 – 393)	317(272 – 536)	332(192 – 393)	277(169 – 432)	188(160 – 320)	4.434≠	0.218
	Range	50 – 862	93–862	173–475	169–432	50–320		
ESR (mm/hour)	Median (IQR)	65 (30 – 90)	70(50 – 95)	60(20 – 90)	52(28 – 130)	90 (30 – 100)	1.057≠	0.787
	Range	10 – 130	13–125	10–90	28–130	30–110		
CRP (mg/L)	Median (IQR)	90 (24 – 220)	87.3(12 – 143)	90(22.9 – 152)	29(24 – 80.9)	250 (220 – 320)	7.602≠	0.055
	Range	0.2 – 368	0.2–368	6–192	24–80.9	12–336		
LDH (IU/L)	Median (IQR)	355.5 (260 – 521)	338(291 – 428)	355(175 – 547)	190(182 – 356)	590(432 – 600)	8.174≠	0.043
	Range	165 – 700	186–548	165–550	182–356	260–700		
D-dimer (mcg/ml)	Median (IQR)	1.55 (0.8 – 5)	0.9(0.6 – 1.7)	2.4(1.4 – 5)	0.9(0.7 – 1.3)	7(3.8 – 9)	13.928 ≠	0.003
	Range	0.2 – 9	0.2–7	0.8–7	0.7–1.3	1.09–9		
Ferritin (µ / L)	Median (IQR)	390 (144 – 1225)	325(94 – 500)	400(300 – 610)	144(55 – 150)	2227(1514 – 2445)	15.222 ≠	0.002
	Range	20 – 3552	20–3552	240–1050	55–150	1225–3200		
ALT (IU/L)	Median (IQR)	33.5 (12 – 72)	19(10 – 35)	32(17 – 55)	10(7 – 51)	80(72 – 100)	12.018 ≠	0.007
	Range	6 – 129	6–90	12–129	7–51	40–120		
BUN (mg/dl)	Mean ± SD	17.80 ± 6.31	15.77±6.67	17.57±2.76	11.67±4.93	24.43±2.94	6.043•	0.003
	Range	5 – 30	5–30	14–22	6–15	20–28		
Creatinine (mg/dl)	Mean ± SD	0.56 ± 0.25	0.54±0.17	0.53±0.33	0.37±0.06	0.73±0.30	1.863•	0.161
	Range	0.3 – 1.2	0.3–0.9	0.3–1.2	0.3–0.4	0.3–1.2		
Total Radiological score	Median (IQR)	4 (0 – 9)	0(0 – 2)	4(3 – 5)	9(9 – 11)	11(6 – 12)	21.251 ≠	0.000
	Range	0 – 16	0–4	3–10	9–11	4–16		

•: One Way ANOVA test; ≠: Kruskal-Wallis test, TLC: Total Leucocytic Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase, ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen.

Table 3: comparison between patients with and without respiratory distress regarding laboratory data and radiological parameters in studied patients.

		No respiratory distress	**Respiratory distress**	**Test value**	**P-value**
		No. = 14	**No. = 16**		
TLC **($x10^3$/u L)**	Mean ± SD	12.40±6.57	12.74±7.62	-0.131•	0.896
	Range	3.7–23	3–23		
Absolute lymphocytic count **($x10^3$/u L)**	Median (IQR)	2.9(2 – 4.43)	2(1.75 – 2.56)	-2.129≠	0.033
	Range	0.4–6.7	0.6–5.8		
Absolute neutrophilic count **($x10^3$/u L)**	Median (IQR)	5.36(4– 14)	8(3.55 – 14.5)	-0.354≠	0.724
	Range	1–18	0.17–19		
Hemoglobin (g/dl)	Mean ± SD	9.58±1.92	10.22±1.34	-1.070•	0.294
	Range	4.9–11.5	7.6–12.8		
Platelets **($x10^3$ /u L)**	Median (IQR)	320.5(272 – 536)	288.5(171 – 338.5)	-1.310≠	0.190
	Range	93–862	50–475		
ESR **(mm/hour)**	Median (IQR)	60(30 – 95)	75(31.5 – 90)	-0.313≠	0.754
	Range	13–125	10–130		
CRP **(mg/L)**	Median (IQR)	88.65(12 – 143)	147(26.5 – 250)	-1.185≠	0.236
	Range	0.2–368	6–336		
LDH **(IU/L)**	Median (IQR)	344(291 – 428)	466(225 – 570)	-1.164≠	0.244
	Range	186–548	165–700		

D-dimer **(mcg/ml)**	Median (IQR)	0.92(0.6 – 2)	3.1(1.2 – 6)	-2.393≠	0.017
	Range	0.2–7	0.7–9		
Ferritin **(µ / L)**	Median (IQR)	347(94 – 500)	607.5(270 – 2063.5)	-1.746≠	0.081
	Range	20–3552	55–3200		
ALT **(IU/L)**	Median (IQR)	21.5(10 – 35)	53.5(24.5 – 85)	-2.287≠	0.022
	Range	6–90	7–129		
BUN **(mg/dl)**	Mean ± SD	15.93±6.44	19.44±5.91	-1.556•	0.131
	Range	5–30	6–28		
Creatinine **(mg/dl)**	Mean ± SD	0.53±0.16	0.59±0.31	-0.703•	0.488
	Range	0.3–0.9	0.3–1.2		
Total Radiological score	Median (IQR)	0(0 – 3)	8.5(4.5 – 11)	-4.385≠	0.000
	Range	0–4	3–16		

•: Independent t-test; ≠: Mann-Whitney test

TLC: Total Leucocytic Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase, ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen.

Table 4: Association between serum amyloid A at presentation with clinical and radiological parameters.

Variables		Serum Amyloid A at presentation (µg / ml)		Test value	P-value
		Median (IQR)	Range		
Oxygen saturation (%)	Normal	360(300−440)	280−560	-2.982•	0.003
	Hypoxic	600(600−610)	280−680		
Blood pressure (mmHg)	Normal	360(300−480)	285−610	7.626≠	0.022
	Hypotension	600(520−600)	280−680		
Respiratory distress	No	310(285−360)	280−440	-3.778•	0.000
	Yes	580(460−600)	285−680		
	Mild	*300(285−360)*	*285−400*		
Clinical severity grades	Moderate	480(440−520)	440−560	*16.373≠*	*0.001*
	Severe	600(600−610)	600−610		
	Critically ill	600(300−610)	280−680		
Chest CT-abnormalities	Absent	345 (292.5 – 372.5)	285 – 400	-2.166•	0.030
	Present	500 (300 – 600)	280 – 680		

•: Mann-Whitney test; ≠: Kruskal-Wallis test

Table 5: correlation between serum amyloid A at presentation with demographic, clinical, laboratory and radiological data of studied patients

	Serum Amyloid A level Day 1 (µg / ml)	
	r	P-value
Age (Years)	-0.196	0.299
Duration of Admission (Days)	-0.002	0.991
Oxygen saturation (%)	-0.563**	0.001**
SBP (mmHg)	-0.557**	0.001**
DBP (mmHg)	-0.555**	0.001**
TLC ($x10^3$/u L)	0.090	0.636
Absolute lymphocytic count ($x10^3$/u L)	-0.153	0.419
Absolute neutrophilic count ($x10^3$/u L)	0.093	0.624
ESR (mm/hour)	-0.069	0.715
CRP (mg/L)	-0.045	0.814
LDH (IU/L)	0.144	0.446
Ferritin (µ / L)	0.145	0.445
ALT (IU/L)	0.328	0.076
D-Dimer (mcg/ml)	0.335	0.070
Number of Affected lung lobes	0.466**	0.010**
Total Radiological score	0.512**	0.004**

r: Spearman correlation coefficient SBP : systolic Blood Pressure, DBP: diastolic blood pressure, TLC: Total Leucocytic Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen

Table 6: Association between follow-up serum amyloid level 10 days after treatment and outcome of studied patients.

		Serum Amyloid A level Day 10 (µg / ml)		Test value	P-value
		Median (IQR)	Range		
Outcome	Survivors	250(190 – 295)	155 – 400	-2.338•	0.019
	Non-survivors	930(840 – 1020)	840 – 1020		

•: Independent t-test

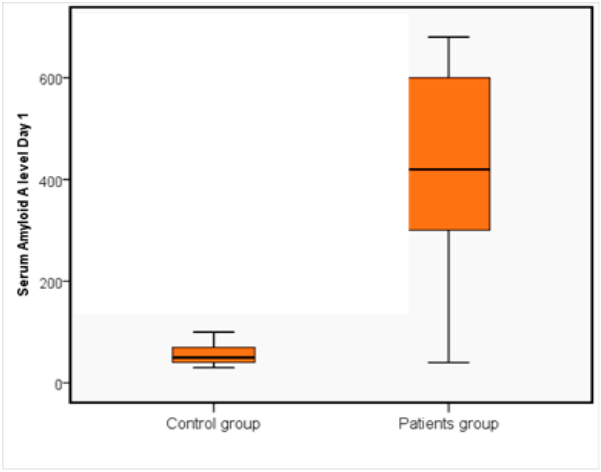

Figure (1): Comparison between patients and controls regarding serum amyloid A level at presentation

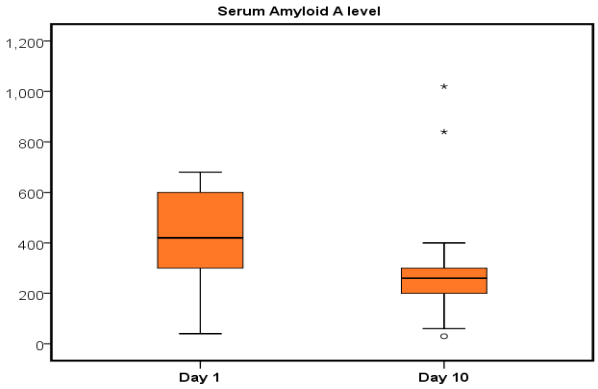

Figure (2): Comparison between serum amyloid A levels at presentation and 10 days after treatment

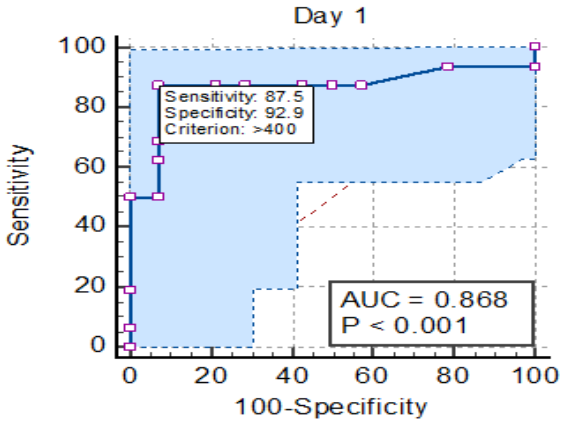

Figure (3): Receiver operating characteristic curve (ROC) for the best cut-off value of serum Amyloid A level to detect radiological abnormalities.

DISCUSSION:

SARS-CoV-2 infection is common in children. However, the burden of illness varies depending on age and underlying co-morbidities. In agreement with our results, de Souza et al[16] and Najafinejad et al[17] reported that the most common symptoms in children are fever and cough, followed by dyspnea. Dyspnea in our study was slightly higher because recruited subjects were hospitalized. The upper respiratory tract is most frequently involved in infected patients. Moreover, Progression to COVID-19 pneumonia with or without hypoxia or acute respiratory distress syndrome has been described. In this work, 53.3% showed signs of respiratory distress, and hypoxia was revealed in 33.3%. Cardiovascular involvement manifested as hypotension was detected in 30% of patients. Driggin et al[18] related vascular collapse to immune-mediated injury secondary to the marked release of inflammatory cytokines. Chest CT can detect COVID-19 pneumonia before clinical symptoms[19]. In a meta-analysis by Nino et al[20], Chest CT was clear in 35.7% of children with COVID-19. Furthermore, radiological findings were detected in 50% of children with dyspnea. This work revealed abnormal radiological findings in 73.3 % of patients on admission. This agreed with Zhang et al[21] where 82% showed positive CT patches. Also, 93.8 % of children with respiratory distress showed positive radiological findings, and the CT severity score was significantly higher compared to those without respiratory distress. Radiological findings and distribution were consistent with previous studies.[22] Serum amyloid A was studied in adult patients with COVID-19 disease. Liu et al[23] reported that high serum SAA can be used as an independent variable for predicting severity of infection. Fu et al[24] and Li et al[13] also concluded that SAA can predict severity and recovery from COVID-19 infection. Pieri et al[12] detected significant persistent elevation of SAA among non survivors compared to survivors. Abdelhakam et al[25] and Li et al[13] reported significant correlation between SAA and severity of radiological involvement. Our findings pointed out a significant increase in serum amyloid A in all children hospitalized with COVID-19. Similarly, Zhang et al[21] reported increase in SAA in 17/20 children with confirmed COVID-19 diagnosis. Also, a significant difference was observed among all categories of clinical severity. This was against Tasar et al[26] who stated that SAA elevation in hospitalized children was not associated with disease severity. Lower airway involvement in children with COVID-19 manifested by respiratory distress and hypoxia was associated with higher SAA levels at presentation. Also, children with increased SAA of more than a cut of 400 ug/ml were more likely to have abnormal CT findings, and in line with adult studies[25], radiological severity was correlated with SAA level. Although SAA level showed a significant decline in children likely to improve after treatment, a progressive increase was noted in deceased children providing an insight into disease prognosis. By contrast to SAA, routinely employed acute phase reactants as CRP and ESR showed no significant difference regarding COVID-19 disease severity grades. Abbas et al[27] reported similar findings. The limitations of this work include small sample size, single-center study, dynamic changes in other inflammatory markers, and radiological findings should have been reported and compared with SAA to confirm accuracy in reflecting disease severity and prognosis.

Conclusions:

Serum amyloid A is a useful indicator for severe COVID-19 disease in children, and it can reflect the severity of radiological involvement, limiting radiation exposure mainly in children with respiratory distress.

Persistent elevation of Serum amyloid A can be utilized as a warning sign for poor outcome.

Declarations:

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

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Author contributions:

E.F. and M.H. contributed to the study conception, design, and supervision. Material preparation, data collection, and analysis were performed by M.M. and M.H. Labs were performed by N.W. Radiology was analyzed by M.A. Resources by M.M. The first draft of the manuscript was written by M.H. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript**.**

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استخدام البروتين النشوى "أ" فى التنبوء بشده اصابه الرئه فى الاشعه المقطعية لدى الاطفال المصابين بفيروس كورونا

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الخلفيه و الهدف من البحث: لقد تم دراسه العديد من المؤشرات الحيويه لتقييم شده و تقدم المرض عند الاصابه بفيروس كورونا. يهدف هذا البحث الى دراسه ديناميكيه البروتين النشوى أ كمؤشر حيوى فى الاطفال المصابين بفيروس كورونا و كذلك علاقته باعراض المرض و شده الاصابه ومدى تأثر الرئه فى الاشعه المقطعيه و التوابع المحتمله للمرض.

المرضى و الطرق: اشتملت هذه الدراسه على ٦٠ طفلا, ٣٠ من المصابين بفيروس كورونا و ٣٠ من الاطفال الاصحاء كمجموعه ضابطه و تم قياس نسبه البروتين النشوى أ فى الدم عند الدخول و فى اليوم العاشر و كذلك عمل اشعه مقطعيه لكل المرضى عند الدخول.

النتائج: تم ايجاد فرق ذو دلاله احصائيه عاليه بالنسبه للبروتين النشوى أ فى اليوم الاول بين المجموعه المصابه و المجموعه الضابطة. تبين ارتفاع نسبه البروتين النشوى أ فى الاطفال المصابين بصعوبه تنفس و قله نسبه الاكسجين بالدم و انخفاض ضغط الدم و الذين لديهم دلالات الاصابه فى الأشعه المقطعيه. وجد فرق ذو دلاله احصائيه فى البروتين النشوى أ بين الاطفال المصابين بدرجات مختلفه من شده المرض. ارتبطت مستويات البروتين النشوى أ بعدد فصوص الرئة المصابه و شده درجة الاصابه فى الاشعه المقطعيه. تبين ارتفاع نسبه البروتين النشوى أ فى الدم فى اليوم العاشر فى الاطفال الذين لم ينجوا من المرض.

الخاتمه: يمكن استخدام البروتين النشوى أ كدلاله على شده الاصابه بفيروس كورونا فى الاطفال . كذلك يمكن الاعتماد عليه فى التبوء بشده الاصابه الرئويه و تقليل الاعتماد على الاشعه المقطعيه خاصه فى الاطفال المصابين بصعوبه فى التنفس.