Original Article

Serum Level of Inflammatory Mediators as Prognostic Biomarkers of Severity of Caustic Injury: A Prospective Study at the Poison Control Center – Ain Shams University Hospitals

Sarah A Eweda[1], Rania Hussien[1], Mohamed Abdel-azim Abdel-aziz[2], Soha Ashry[1]

[1]*Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Ain Shams University*

[2]*Fellow in Poison Control Center, Ain Shams University Hospitals*

Corresponding author:

Sarah A Eweda

E-mail:

only.sms@hotmail.com

Orchid ID

0000-0002-8135-6396

ABSTRACT

Background: Caustic injury, caused by the ingestion of corrosive substances, is a serious health concern worldwide due to its high morbidity and mortality rate. **Aim:** The present study aimed to investigate the possible role of serum levels of inflammatory mediators namely cortisol, C-reactive protein (CRP) and alpha 1 antitrypsin (AAT) in the detection of the severity of corrosive ingestion. **Methods**: This prospective study was conducted through collecting demographic, clinical data and blood samples from 30 patients with corrosive ingestion admitted to the Poison Control Centre of Ain Shams University Hospitals. Complete blood count (CBC), serum levels of inflammatory mediators were analyzed at 24 and 72 hours post ingestion. Follow up of the patients was done at the outpatient clinic for three weeks for development of strictures. **Results:** The studied patients were 13 females (43.3 %) and 17 males (56.7 %) whose mean age was 2.7±1.26 years. Twenty patients were admitted to the inpatient wards and ten patients were admitted to the intensive care unit (ICU). The presence of hematemesis, respiratory distress, metabolic acidosis on admission and the formation of stricture and extended hospital stay were significantly higher in the ICU group than the inpatient group. A significantly higher level of CRP and AAT was detected in the ICU group, and the high levels of both mediators correlated with the prolonged duration of hospital stay. AAT level greater than 179ng/ml at 24 hours was significantly associated with the formation of strictures. **Conclusion:** This study provides evidence supporting the potential role of CRP and AAT as reliable biomarkers in predicting the severity and outcome of caustic ingestion. Moreover, a cut-off value of AAT serum level of 179 ng/ml is considered for predicting the susceptibility of formation of strictures in patients with corrosive ingestion, hence directing treatment for better patient outcomes.

Keywords: Caustic injury, Corrosives, Cortisol, C-reactive protein, Alpha 1-Antitrypsin

I. INTRODUCTION:

Caustic injury, caused by the ingestion of corrosive substances, is a serious health concern worldwide, particularly in low- and middle-income countries where access to these substances is relatively unrestricted (Chibishev et al., 2013). Ingestion of such substances can lead to severe complications, including esophageal stricture, perforation, and long-term risks of esophageal and gastric cancer (Contini and Scarpignato, 2013; Kluger et al., 2015). The severity of damages to the gastrointestinal tract is related to the caustic type, amount, and concentration (Hall et al., 2019). Early diagnosis and prompt management are crucial to minimize associated morbidity and mortality (Kamat et al., 2019). Esophagogastroscopy, and alternatively, computerized tomography scan of the chest and abdomen with Zargar's classification for staging, has been used to diagnose and estimate the severity of damage (Lurie et al., 2013). However, determining the severity of caustic injury remains challenging, as clinical symptoms do not always correlate with the extent of damage to the esophagus and surrounding tissues (Raynaud et al, 2016). Inflammatory mediators play an important role in the body's response to injury. They also play an important role in the pathophysiology of caustic injury, as they modulate the inflammatory response and tissue damage following exposure to corrosive substances. Thus, they can potentially serve as prognostic biomarkers to predict the severity of caustic injury (Park, 2014). However, despite the growing body of evidence supporting the role of inflammatory mediators as prognostic biomarkers in caustic injury, some limitations persist in the literature. Factors such as variability in study designs and timing of biomarker measurements may contribute to the different conclusions across studies. In addition, the potential additive, or synergistic effects of multiple inflammatory mediators in predicting the severity of caustic injury is not fully explored, pointing out to a need for further investigation (Chirica et al., 2015). Therefore, this study aimed to investigate the association between serum levels of inflammatory mediators namely cortisol, c-reactive protein (CRP) and alpha 1 antitrypsin (AAT) and the severity of caustic injuries aiming to assess their possible role in the early detection of the severity of corrosive ingestion in order to help direct clinical decision makers to effective treatment strategies.

II. PATIENTS AND METHODS:

Study Design: A prospective cohort study.

Study population: Patients with a diagnosis of corrosive ingestion admitted to the Poison Control Center – Ain Shams University Hospitals (PCC- ASUH) from from the beginning of July 2022 till end of December 2022. Diagnosis of corrosive ingestion was based on history of ingestion and clinical findings such as vomiting, hematemesis, oropharyngeal burns, lip edema, dysphagia, epigastric pain, drooling or respiratory distress. The serum levels of inflammatory mediators were assessed at different time points. Correlations between the serum levels of inflammatory mediators and injury severity was analyzed to identify potential prognostic biomarkers.

Exclusion Criteria: - The following patients were excluded from the study:

-Patients with delay time more than 48 hours.

-Asymptomatic patients

-Patients with known diagnosis of any gastrointestinal inflammatory condition.

-Patients with congenital esophageal disorders.

-Patients with pre-existing inflammatory diseases

-Patients with severe medical comorbidities

Sample Size: By using Power Analysis and Sample Size software (PASS 15) (Version 15.0.10) for sample size calculation, setting confidence level at 95%, at margin of error ± 0.15 and after assuming that the correlation between serum level of inflammatory mediators and the severity of caustic injury in patients with corrosive ingestion is (r= 0.80); based on that and after considering 10% dropout rate, a sample size of at least 30 patients with corrosive ingestion will be sufficient to achieve the study objective.

Patient groups:

Patients included in the current study with corrosive ingestion were divided into two groups:

Group (1) Inpatient group: Those who were admitted and treated in inpatient wards

Group (2) Intensive care unit (ICU) group: Those who were admitted and treated in the intensive care unit

Data Collection Tools:

- Data extraction sheet was used to record the required data which included:
- Patient demographics (age, sex), medical history, intoxication data (type of caustic agent, manner of poisoning, delay time between corrosive ingestion

and medical consultation, pre-treatment) and presenting symptoms.

- Clinical examination on admission which included general examination, gastrointestinal, cardiovascular, and respiratory system examination.
- The selected patients were followed up at the outpatient clinic for three weeks for development of stricture that is defined by dysphagia which was confirmed by a barium study 21 days after corrosive ingestion. Any complications observed during follow-up were recorded, as well as clinical outcomes.

Laboratory investigations:

Venous blood samples were collected from each patient twice at 9 Am.One sample after 24 hours of corrosive ingestion and the other one after 72 hours. The blood sample was divided into two parts; one was anticoagulated with EDTA for analysis of complete blood count (CBC) and the other part was transferred to a clean dry centrifuge tube and left for 30 minutes to clot. After complete clotting, it was centrifuged for 10 minutes at 4000 rpm. The serum was separated for analysis of cortisol, CRP, and AAT.

Chemicals and reagents:

-The complete blood count was done using Sysmix xn1000 automated hematology analyzer. In addition, a blood film was examined.

Serum cortisol was determined by immunoassay technique using the ab108665Cortisol and ELISA Kit BioTek ELISA reader.

-C-reactive protein level was determined by the semi-quantitative latex agglutination test using the Spinreact CRP- Latex slide agglutination. Reference range: up to 6 mg/L (Lee et al., 2013).

-Alpha 1 antitrypsin was determined by immunoassay technique using the ab189579 – Human alpha 1 Antitrypsin SimpleStep ELISA® Kit and ELISA Kit BioTek ELISA reader.

Data management and Statistical analysis:

Data was collected, tabulated, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations for parametric distribution and median and interquartile ranges for non-parametric distribution. Qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test while with non-parametric data, they were done by using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Regression analysis was used to identify trends and associations between variables.

Ethics Considerations: Approval was obtained from the research ethics committee at the faculty of medicine, ASU number FMASU R129/2023. Informed consent was collected from patients' guardians and privacy of data throughout the study was maintained.

III. RESULTS:

The present study included a total of 30 children with a mean age of 2.7±1.26 years. 43.3% were females and 56.7% were males. The inpatient group comprised 20 (66.7%) patients and the ICU group comprised 10 (33.3%). (Table 1) shows that there was no significant difference ($p > 0.05$) in age and gender distribution as well as the type of ingested corrosive substance, the presence of vomiting or dysphagia between the inpatient and ICU groups. However, the incidences of hematemesis, respiratory distress, metabolic acidosis, length of hospital stay and stricture formation were significantly higher in the ICU group than in the inpatient group ($p < 0.001$, $p < 0.002$, $p < 0.002$, $p < 0.005$, $p < 0.002$ respectively)**.** (Table 2) shows that cortisol and AAT levels at 24 hours showed no significant differences between the two groups, with median cortisol values of 15.6 and 24.7, and mean AAT values of 159.2 and 190.7 for the inpatient and ICU groups respectively. However, a significant difference was noted in CRP levels, with the ICU group presenting higher levels ($p<0.05$). No significant differences were noted for white blood cell count and hemoglobin levels between the two groups.

(Table 3) shows that the median cortisol and CRP levels at 72 hours in both groups were not significantly different. However, AAT levels were significantly higher in the ICU group. No significant differences were noted for white blood cell count and hemoglobin levels between the two groups. (Table 4) presents the correlation between laboratory parameters and the duration of hospital stay for all patients at 24 hours post-ingestion. There was a moderate positive correlation among the levels of cortisol and AAT, and they both exhibited a strong positive

correlation with CRP. Both AAT and CRP showed a significant positive correlation with the duration of hospital stay. However, the white blood cell count (WBC) and hemoglobin (Hb) levels showed no significant correlation with any of the other studied parameters or with hospital stay duration. (Table 5) illustrates the correlation between laboratory parameters and the length of hospital stay for all patients at 72 hours post-ingestion. AAT and CRP levels showed a statistically significant correlation with hospital stay duration, while WBC count showed moderate correlation. Hb levels did not correlate with any of the studied parameters or hospital stay duration. (Table 6) shows the univariate and multivariate logistic regression analysis for factors associated with stricture formation. The univariate analysis showed an association between ICU admission, high levels of AAT at 24 hours (>179 ng/ml), and elevated CRP at 24 hours (>6 mg/L) as well as the length of hospital stay more than 5 days and the formation of stricture. The multivariate analysis, showed that AAT at 24 hours (>179 ng/ml) and ICU admission still showed an association with stricture formation.

Table (1): Comparison between the studied groups with corrosive ingestion admitted to the poison control center, ASUH regarding patient characteristics

Patients' characteristics		Total number of patients=30	Group (1)* No. = 20	Group (2)* No. = 10	Test value	P-value	Sig.
Age (years)#	Mean±SD	2.7±1.26	2.85±1.29	2.5±1.29	0.55	0.591	NS
Gender ^	Female	13 (43.3%)	10 (50.0%)	3 (30.0%)	1.086	0.297	NS
	Male	17 (56.7%)	10 (50.0%)	7 (70.0%)			
Main type of corrosive ^	Acid	12 (40.0%)	7 (35.0%)	5 (50.0%)	0.625	0.429	NS
	Alkali	18 (60.0%)	13 (65.0%)	5 (50.0%)			
Vomiting ^	No	12 (40.0%)	10 (50.0%)	2 (20.0%)	2.500	0.114	NS
	Yes	18 (60.0%)	10 (50.0%)	8 (80.0%)			
Hematemesis ^	No	23 (76.7%)	20 (100.0%)	3 (30.0%)	18.261	0.001	HS
	Yes	7 (23.3%)	0 (0.0%)	7 (70.0%)			
Dysphagia ^	No	13 (43.3%)	11 (55.0%)	2 (20.0%)	3.326	0.068	NS
	Yes	17 (56.7%)	9 (45.0%)	8 (80.0%)			
Respiratory distress ^	No	26 (86.7%)	20 (100.0%)	6 (60.0%)	9.231	0.002	HS
	Yes	4 (13.3%)	0 (0.0%)	4 (40.0%)			
Metabolic acidosis ^	No	26 (86.7%)	20 (100.0%)	6 (60.0%)	9.231	0.002	HS
	Yes	4 (13.3%)	0 (0.0%)	4 (40.0%)			
Hospital stay duration (days)#	Median (IQR)	4 (3 – 7)	4 (3 - 4.5)	8 (6 - 10)	-2.796	0.005	HS
	Range	2 – 17	2 – 8	2 – 17			
Stricture formation ^	No stricture	18 (60.0%)	16 (80.0%)	2 (20.0%)	10.000	0.002	HS
	Stricture	12 (40.0%)	4 (20.0%)	8 (80.0%)			

ASUH: Ain Shams University Hospitals * Groups included in the statistical analysis
Group (1): Inpatient group
Group (2): Intensive care unit (ICU) group
^ Chi square test was used #Mann-Whitney test was used, NS: Non-significant S: Significant HS: Highly significant
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant. No.: number
Number of studied patients= 35, SD: Standard Deviation

Table (2): Comparison between the studied groups with corrosive ingestion admitted to the poison control center, ASUH regarding laboratory parameters measured at 24 hours post ingestion

Laboratory parameters		Group (1) No. = 20	Group (2) No. = 10	Test value	P-value	Sig.
Cortisol (mcg/dl) #	Median (IQR) Range	15.6 (10.9 - 26.45) 6.4 – 65.9	24.7 (19.1 - 29.9) 6.2 – 34.5	-1.166	0.244	NS
Alpha 1 antitrypsin (ng/ml) *	Mean±SD Range	159.2 ± 33.36 112 – 228	190.7 ± 41.96 134 – 250	-1.848	0.065	NS
C-reactive protein (mg/L) #	Median (IQR) Range	0 (0 - 12) 0 – 48	24 (12 - 32) 0 – 96	-2.005	0.045	S
White blood cells (number/mm^3) #	Median (IQR) Range	10600 (8350 - 13425) 3700 – 19400	9500 (6000 - 14000) 5700 – 27800	-0.220	0.826	NS
Hemoglobin (g/dl) *	Mean±SD Range	12.02 ± 1.22 9.8 – 14.1	12.76 ± 1.64 10.4 – 15.3	-0.883	0.377	NS

ASUH: Ain Shams University Total number of patients=30
Group (1): Inpatient group
Group (2): Intensive care unit (ICU) group
* Independent t-test was used #Mann-Whitney test was used
NS: Non-significant, S: Significant, HS: Highly significant
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.
No.: number

Table (3): Comparison between the studied groups with corrosive ingestion admitted to the poison control center, ASUH regarding laboratory parameters measured at 72 hours post ingestion

Laboratory parameters		Group (1) No. = 20	Group (II) No. = 10	Test value	P-value	Sig.
Cortisol (mcg/dl) #	Median (IQR) Range	14.85 (10.6 - 21.1) 4.8 – 28	20.55 (15 - 25) 6.5 – 52.2	-1.321	0.187	NS
Alpha 1 antitrypsin (ng/ml) *	Mean±SD Range	190.4 ± 44.51 127 – 264	236.5 ± 27.99 188 – 280	-2.685	0.007	HS
C-reactive protein (mg/L) #	Median (IQR) Range	9 (6 - 24) 0 – 96	24 (12 - 48) 6 – 96	-1.963	0.051	NS
White blood cells (number/mm^3) #	Median (IQR) Range	8100 (6050 - 10650) 3600 – 12500	8650 (6200 - 11300) 5500 – 12000	-0.462	0.644	NS
Hemoglobin (g/dl) *	Mean±SD Range	11.17 ± 1.31 9 – 12.8	10.84 ± 1.48 7.9 – 12.6	-0.397	0.692	NS

ASUH: Ain Shams University Total number of patients=30
Group (1): Inpatient group, Group (2): Intensive care unit (ICU) group
* Independent t-test was used #Mann-Whitney test was used
NS: Non-significant S: Significant HS: Highly significant
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.
No.: number

Table (4): Spearman correlation between the studied laboratory parameters and hospital stay of the 30 patients included in the study with corrosive ingestion admitted to the poison control center, ASUH at 24 hours

Laboratory parameters	Cortisol (mcg/dl)		AAT (ng/ml)		CRP (mg/L)		WBC (number/mm^3)		Hb (g/dl)		Hospital stay (days)	
	r	P	R	P	R	P	r	P	r	P	r	P
Cortisol (mcg/dl)			.427*	0.019	.586**	0.001	0.020	0.914	0.125	0.509	0.242	0.207
AAT (ng/ml)	.427*	0.019			.666**	0.000	-0.025	0.894	0.099	0.602	0.556**	0.002
CRP (mg/L)	.586**	0.001	.666**	0.000			0.145	0.443	0.060	0.752	0.642**	0.000
WBC (number/mm^3)	0.020	0.914	-0.025	0.894	0.145	0.443			0.096	0.612	0.163	0.398
Hb (g/dl)	0.125	0.509	0.099	0.602	0.060	0.752	0.096	0.612			0.184	0.341
Hospital stay (days)	0.242	0.207	0.556**	0.002	0.642**	0.000	0.163	0.398	0.184	0.341		

ASUH: Ain Shams University Hospitals, Total number of patients=30
AAT: Alpha 1 antitrypsin, CRP: C-reactive protein, WBC: White blood cells, Hb: Hemoglobin
r-value 0.0-0.3: no to mild correlation r-value 0.3-0.5: Moderate correlation; r-value 0.5-1.0: high correlation
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (5): Spearman correlation between the studied laboratory parameters and hospital stay of the 30 patients included in the study with corrosive ingestion admitted to the poison control center, ASUH at 72 hours

Laboratory parameters	Cortisol (mcg/dl)		AAT (ng/ml)		CRP (mg/L)		WBC (number/mm^3)		Hb (g/dl)		Hospital stay (days)	
	r	P	R	P	R	P	r	P	r	p	r	p
Cortisol (mcg/dl)			0.360	0.051	0.244	0.193	0.141	0.456	-0.043	0.823	0.215	0.262
AAT (ng/ml)	0.360	0.051			.502**	0.005	0.094	0.623	-0.226	0.229	0.480**	0.008
CRP (mg/L)	0.244	0.193	.502**	0.005			-0.147	0.438	-0.256	0.173	0.566**	0.001
WBC (number/mm^3)	0.141	0.456	0.094	0.623	-0.147	0.438			0.112	0.556	0.383*	0.041
Hb (g/dl)	-0.043	0.823	-0.226	0.229	-0.256	0.173	0.112	0.556			0.040	0.838
Hospital stay (days)	0.215	0.262	0.480**	0.008	0.566**	0.001	0.383*	0.041	0.040	0.838		

ASUH: Ain Shams University Hospitals, Total number of patients=30
AAT: Alpha 1 antitrypsin, CRP: C-reactive protein, WBC: White blood cells, Hb: Hemoglobin
r-value 0.0-0.3: no to mild correlation, r-value 0.3-0.5: Moderate correlation; r-value 0.5-1.0: high correlation
P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

Table (6): Univariate and multivariate logistic regression analysis for factors associated with stricture formation for the 30 patients included in the study with corrosive ingestion admitted to the poison control center, ASUH

Tested parameters	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Hospital stay >5 days	**0.007**	14.000	2.061	95.085	–	–	–	–
Intensive care unit admission	**0.004**	16.000	2.399	106.731	**0.046**	10.005	1.042	96.084
Alpha 1 antitrypsin at 24 hours > 179 (ng/ml)	**0.003**	34.000	3.253	355.409	**0.018**	22.22	1.71	288.781
C-reactive protein at 24 hours > 6 (mg/L)	**0.006**	13.000	2.074	81.479	–	–	–	–

ASUH: Ain Shams University Hospitals Total number of patients=30
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

IV. DISCUSSION:

Caustic injury is a significant health concern due to its high morbidity and mortality rate. Prompt evaluation and management are emphasized in order to stop the development of injury and prevent the progression of complications (De Lusong et al., 2017; ELHelaly et al., 2022). The current study investigated the possible role of inflammatory mediators as prognostic biomarkers of the severity of caustic injury, aiming to aid in identifying cases with possible deterioration to tailor the provided treatment and improve outcomes. The study comprised 30 patients admitted to the Poison Control Center, ASUH with caustic injury. The studied patients were admitted and treated either in the inpatient wards (20 patients) or the ICU (10 patients).Stricture formation observed in the follow-up of patients after three weeks and the longer duration of hospital stay documented in the current study were significantly higher in the ICU group when compared to the inpatient group, reflecting poor outcome in these patients. Similarly, Vijay Kumar et al., 2019 reported that severe and complicated cases of caustic ingestion are more prone to stricture formation, and they often need prolonged hospital stay. Cheng et al., 2021 recorded in their study an increase in the number of cases with stricture formation among the severely affected group with corrosive ingestion.

Caustic injury of the gastrointestinal tract mucosa is an acute insult which is associated with a high degree of systemic inflammation. Inflammatory mediators have been implicated in the pathophysiology of caustic injury, as they modulate the inflammatory response and tissue damage following exposure to corrosive substances. As reported by previous studies, the stress of the tissue damage produces rapid immune response and activates the stress hormone and acute phase reactants (Nam et al., 2015; Cheng et al., 2021). Stress hormone or cortisol is known to increase in conditions of stress in order to help the body to react. Acute phase reactants are inflammation markers that exhibit significant changes in serum concentration during inflammation and tissue injury. They include C-reactive protein, Alpha-1 antitrypsin in addition to other proteins and cytokines (Lee et al., 2015; Bray et al., 2016). The current study was set to explore the potential of serum inflammatory mediators to predict the severity of caustic injury in order to guide therapeutic interventions. Laboratory parameters were compared between the two groups (inpatient and ICU) at 24 and 72 hours post-ingestion. While there were no significant differences in the cortisol, Hb levels and WBC, between the studied groups, a significantly higher level of CRP than normal values was detected in the ICU group 24 hours after ingestion. In addition, the AAT level was significantly higher in the ICU group at 72 hours post ingestion. This points to a possible role of these markers in predicting the severity of the corrosive injury as they are higher in severely affected patients in the ICU group.

Cortisol is a glucocorticoid hormone secreted by the adrenal glands. It regulates the body's stress response, suppresses inflammation, controls metabolism, regulates blood pressure and blood sugar and controls sleep-wake cycle. Normally, the level of serum cortisol peaks in the early morning (10-20 mcg/dl) and declines throughout the day (3-10 mcg/dl), reaching its lowest level around midnight. During acute stress response, cortisol level increases and could reach 10-20 times its normal level within minutes but also decreases quickly as its half-life is around 60-90 minutes (Jung et al., 2014). This explains the insignificance of its elevated levels when compared between the two groups in the current study.

C-reactive protein is an acute-phase inflammatory plasma protein that increases up to 1,000-fold at sites of infection or inflammation. CRP is synthesized primarily in liver hepatocytes and it plays important

roles in inflammatory processes and host responses to infection. The average levels of CRP in serum are around 0.8 mg/L. Following severe tissue damage, CRP plasma levels increase from around 1 µg/mL to over 500 µg/mL within 24–72 h. After resolution, CRP values decrease over 18–20 hours, close to its half-life (Sproston and Ashworth, 2018). This pattern explains the significance of its elevated levels at 24 hours when compared between the two groups in the current study.Alpha-1 antitrypsin is a plasma glycoprotein produced mainly by hepatocytes and is abundant in plasma with a mean concentration of 1.3 g/L (range 0.9–1.75 g/L) and a plasma half-life of 4–5 days (O'Brian et al., 2022). AAT is an acute phase protein whose levels are elevated within hours of developing inflammation. It has a key role in innate immune defense and during the acute-phase protein response where its plasma concentration can rise to between two and four-folds leading to regulation of inflammation (Lockett et al., 2013; McCarthy et al., 2014).

AAT can also mediate anti-inflammatory effects through the modulation of TNF α signaling. By that, it promotes an initial augmented response to inflammation in the acute phase followed by selective inhibition later, thereby supporting resolution of chronic inflammation (Bergin et al., 2014). This pattern and mechanism of action explains the significance of its elevated levels at 72 hours when compared between the two groups in the current study. In addition, it highlights the possibility of considering the level of AAT as an indicator of the severity of caustic injury that could be used throughout the stage of disease. In the current study, correlation analysis was done to the laboratory parameters both at 24 and 72 hours post corrosive ingestion. At 24 hours the cortisol and AAT levels showed a moderate positive correlation, indicating that as the levels of one parameter increased, so did the levels of the other. Furthermore, both cortisol and AAT exhibited a strong positive correlation with CRP, suggesting that higher levels of these biomarkers were associated with increased inflammation. In addition, both AAT and CRP showed a significant positive correlation with the duration of hospital stay, indicating that higher levels of these biomarkers were associated with longer hospital stays echoing the findings of previous research (Park, 2014; Vijay Kumar et al., 2019) This emphasizes the potential prognostic value of cortisol, AAT, and CRP levels in patients with caustic injuries. Interestingly at 72 hours post-ingestion, there was a moderate, though not

statistically significant, correlation between cortisol and AAT levels. AAT maintained a statistically significant correlation with hospital stay duration, emphasizing its potential role as a delayed biomarker of severity. CRP levels were also significantly correlated with the duration of hospital stay. Overall, these results reinforce the potential of AAT, CRP, as indicators of severity in caustic injuries. These results suggest that these biomarkers could potentially be useful in assessing the severity of caustic injuries. Similar findings were recorded by other studies that investigated the association between serum levels of inflammatory mediators and the severity of caustic injury. Cheng et al., 2021 reported that the tissue damage by caustic injuries produces an immune response syndrome with elevation of various inflammatory markers. They emphasized that the level of elevation of those markers correlates with the degree of severity of cases. Park, 2014 reported an increase in CRP levels which were found to be significantly associated with the extent of esophageal injury and the need for surgical intervention in patients with caustic ingestion. The formation of esophageal stricture is one of the worst outcomes of caustic injury that is often accompanied by long-term undernourishment and compromised nutritional outcome. It has deleterious effects on the quality of life and the long term survival of patients (Vezakis et al., 2016; Katibe et al., 2018). Accordingly, the current study considered the potential of inflammatory markers to point out vulnerable cases to stricture formation. The results of the regression analysis for factors associated with the development of strictures revealed that a hospital stay longer than 5 days, ICU admission, an AAT level greater than 179 ng/ml at 24 hours, and a CRP level higher than 6 mg/L at 24 hours were all significantly associated with the formation of strictures. In the multivariate analysis which provides a more comprehensive understanding of the factors associated with the development of stricture, because it considers the complex interactions between multiple factors, only ICU admission and an AAT level higher than 179 ng/ml at 24 hours maintained their significance which implies that patients admitted to the ICU and those with an AAT level above 179 ng/ml at 24 hours were more likely to develop strictures. These findings indicate the predictive value of these variables in assessing the risk of stricture formation following caustic ingestion and they highlight the potential role of these

parameters as prognostic markers for severe outcomes. Previous research documented the increased liability of esophageal stricture formation in the severely affected patient groups with corrosive ingestion (Urganci et al., 2014; Cowan et al., 2017).In addition, the current regression analysis revealed that a level of 179 ng/ml of AAT is considered a cut-off value at 24 hours post-ingestion to predict the susceptibility of stricture formation in patients with corrosive ingestion. This finding will aid in early identification of high-risk patients and will facilitate timely and appropriate therapeutic interventions, ultimately improving patient outcomes. The study reveals valuable information that may contribute to early identification of high-risk patients following caustic ingestion, ultimately leading to improved management and better patient outcomes. However, the study is limited by its small sample size, and future larger, multicenter studies are needed to validate these findings.

V. CONCLUSION and RECOMMENDATIONS:

In conclusion, the current study suggests that inflammatory mediators namely cortisol, CRP and AAT could be promising prognostic biomarkers for assessing the severity of caustic injuries. Although serum levels of cortisol fade early, yet the serum levels of both CRP and AAT are considered reliable biomarkers in predicting the severity and outcome of caustic ingestion in the course of the disease. Additionally, the level of AAT is the marker of choice throughout the course of illness. More importantly, a cut-off value of AAT serum level of 179 ng/ml is considered for predicting the susceptibility of formation of strictures in patients with corrosive ingestion, hence directing treatment for better patient outcome .The current study recommends the augmentation of initiatives directed towards prevention of caustic injuries as it remains to be the best approach to reduce the morbidity and mortality caused by caustic ingestion.

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VII. Conflict of interest:

The authors declare that there is no conflict of interest.

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IX. References

- Bergin DA, Reeves EP, Hurley K,Wolfe R, Jameel R, Fitzgerald S, McElvaney NG. (2014): The circulating proteinase inhibitor α-1 antitrypsin regulates neutrophil degranulation and autoimmunity. Sci. Transl. Med. 6, 217.
- Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, Yale SH. (2016): Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine. WMJ. 115(6):317-21.
- Cheng H-T, Seak C-J, Cheng C-C, Chen TH, Sung C-M, Kang S-C, Chen Y-J, Ng C-J, Lee C-W, Huang S-W, Huang H-C, Yen T-H. (2021): Profiling of inflammatory cytokines in patients with caustic gastrointestinal tract injury. PLoS ONE 16(11): e0260012. https://doi.org/10.1371/journal. pone.0260012
- Chibishev A, Pereska Z, Chibisheva V, Simonovska, N. (2013): Caustic poisonings in adults. Mater Sociomed, 24(2):125-30.doi: 10.5455/msm.2012.24.125-130.
- Chirica M, Bonavina L, Kelly MD, Sarfati E, Cattan P. (2015): Caustic ingestion. Lancet. 26;386(10000):1720-31.
- Contini S and Scarpignato C. (2013): Caustic injury of the upper gastrointestinal tract: a comprehensive review. World Journal of Gastroenterology, 19(25), 3918-3930. doi: 10.3748/wjg.v19.i25.3918.
- Cowan T, Foster R, Isbister GK. (2017): Acute esophageal injury and strictures following corrosive ingestions in a 27year cohort. Am J Emerg Med. 35(3):488-492.doi:10.1016/j.ajem.2016.12.002.
- De Lusong MAA, Timbol ABG, Tuazon DJS. (2017): Management of esophageal caustic injury. World J Gastrointest Pharmacol Ther. 8(2):90-98. doi: 10.4292/wjgpt.v8.i2.90.
- Elawady EH, Hafiz RN, Nasr MA. (2017): The Prognostic Value Of Some Initial Clinical Manifestations And Biochemical Parameters For Evaluating The Outcome In Corrosives Poisoned Children. Zagazig J. Forensic Med. & Toxicol. 15(1):14-28
- ELHelaly H, Radwan AB, Ghanem WA, Gad-Allah MA, Zaki AM (2022): The Impact of Initial Management for

Pediatric Corrosive Ingestion in a Specialized Toxicology Center "Poison Control Center Ain Shams University Hospitals" (PCCASUH) on Long Term Outcome of Corrosive Ingestion Sequels. Zagazig J. Forensic Med. & Toxicol. 20(1):210-224

- Hall AH, Jacquemin D, Henny D, Mathieu L, Josset P, Meyer B. (2019): Corrosive substances ingestion: a review. Crit Rev Toxicol. 2019; 49(8):637–69. doi:10.1080/10408444.2019.1707773
- Jung C, Greco S, Nguyen HH, Ho JT, Lewis JG, Torpy DJ, Inder WJ. (2014):Plasma, salivary and urinary cortisol levels following physiological and stress doses of hydrocortisone in normal volunteers. BMC Endocr Disord 14,91.https://doi.org/10.1186/1472-6823-14-91
- Kalayarasan R, Ananthakrishnan N, Kate V. (2019): Corrosive Ingestion. Indian J Crit Care Med. 23(Suppl 4):S282-S286. doi: 10.5005/jp-journals-10071-23305.
- Kamat R, Gupta P, Reddy YR, Kochhar S, Nagi B, Kochhar R. (2019): Corrosive injuries of the upper gastrointestinal tract: A pictorial review of the imaging features. Indian J Radiol Imaging. 29(1):6-13. doi: 10.4103/ijri.IJRI_349_18.
- Katibe R, Abdelgadir I, McGrogan P, Akobeng AK. (2018): Corticosteroids for Preventing Caustic Esophageal Strictures: Systematic Review and Meta-analysis. J Pediatr Gastroenterol Nutr. 66(6):898–902. doi: 10.1097/MPG.0000000000001852.
- Kluger Y, Ishay OB, Sartelli M, Katz A, Ansaloni L, Gomez CA, Biffl W, Catena F, Fraga GP, Di Saverio S, Goran A, Ghnnam W, Kashuk J, Leppäniemi A, Marwah S, Moore EE, Bala M, Massalou D, Mircea C, Bonavina L.(2015):Caustic ingestion management: world society of emergency surgery preliminary survey of expert opinion. World J Emerg Surg. 2015 Oct 16;10:48. doi: 10.1186/s13017-015-0043-4. Erratum in: World J Emerg Surg. 10:56.
- Le Naoures P, Hamy A, Lerolle N, Métivier E, Lermite E, Venara A (2017): Risk factors for symptomatic esophageal stricture after caustic ingestion-a retrospective cohort study, Diseases of the Esophagus. 30(6):1-6
- Lee DY, Kim E, Choi MH. (2015): Technical and clinical aspects of cortisol

as a biochemical marker of chronic stress. BMB Rep. 48(4):209-16.

- Lockett AD, Kimani S, Ddungu G, Wrenger S, Tuder RM, Janciauskiene SM, Petrache I. (2013): α1-antitrypsin modulates lung endothelial cell inflammatory responses to TNF- α. Am. J. Respir. Cell Mol. Biol. 49, 143–150.
- Lurie Y, Slotky M, Fischer D, Shreter R, Bentur Y. (2013): The role of chest and abdominal computed tomography in assessing the severity of acute corrosive ingestion. Clin Toxicol (Phila). 51(9):834–7.
- McCarthy C, Saldova R, Wormald MR, Rudd PM, McElvaney NG, Reeves EP (2014): The Role and Importance of Glycosylation of Acute Phase Proteins with Focus on Alpha-1 Antitrypsin in Acute and Chronic Inflammatory Conditions. Journal of Proteome Research 13 (7), 3131-3143. DOI: 10.1021/pr500146y
- Nam SY, Choi IJ, Ryu KH, Park BJ, Kim YW, Kim HB, Kim JS. (2015):The effect of abdominal visceral fat, circulating inflammatory cytokines, and leptin levels on reflux esophagitis. J Neurogastroenterol Motil. 21(2):247-54. doi: 10.5056/jnm14114.
- O'Brien ME, Murray G, Gogoi D, Yusuf A, McCarthy C, Wormald MR, Casey M, Gabillard-Lefort C, McElvaney NG, Reeves EP. (2022): A Review of Alpha-1 Antitrypsin Binding Partners for Immune Regulation and Potential Therapeutic Application. Int. J. Mol. Sci. 23, 2441. https://doi.org/10.3390/ijms23052441
- Park KS. (2014): Evaluation and management of caustic injuries from ingestion of Acid or alkaline substances. Clin Endosc. 47(4):301-7. doi: 10.5946/ce.47.4.301.
- Raynaud K, Seguy D, Rogosnitzky M, Saulnier F, Pruvot FR, Zerbib P. (2016): Conservative management of severe caustic injuries during acute phase leads to superior long-term nutritional and quality of life (QoL) outcome. Langenbecks Arch Surg. 401(1):81–7. doi: 10.1007/s00423-015-1366-z.
- Sproston NR and Ashworth JJ. (2018): Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 9:754. doi: 10.3389/fimmu.2018.00754.
- Urganci N, Usta M, Kalyoncu D, Demirel E. (2014): Corrosive substance ingestion in children. Indian J Pediatr.

81(7):675-9. doi: 10.1007/s12098-013-1170-0.

– Vezakis AI, Pantiora EV, Kontis EA, Sakellariou V, Theodorou D, Gkiokas G, Polydorou AA, Fragulidis GP. (2016): Clinical Spectrum and Management of Caustic Ingestion: A Case Series Presenting Three Opposing Outcomes. Am J Case Rep. 17:340-6. doi: 10.12659/ajcr.897778.

– Vijay Kumar TR, Anil Kumar G, Nandeesh HP, Deepak Suvarna, Aradya HV, Anurag Lavekar, Rithesh Reddy. (2019): Clinico-Endoscopic Profile and Outcome of Corrosive Ingestion: A Single Centre Experience from a Tertiary Care Hospital in Southern India. Surg. Gastroenterol. Oncol. 24(4):191-196.

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الملخص العربي

مستوى دلالات الالتهاب كمؤشرات بيولوجية تنبؤية لشدة الإصابة بالمواد الكاوية ؛ دراسة مستقبلية بمركز علاج التسمم ـ مستشفيات جامعة عين شمس

ساره عاطف عويضه١، رانيا حسين١، محمد عبد العظيم عبد العزيز٢، سهي خالد عشري١

قسم الطب الشرعي والسموم الإكلينيكية، كلية الطب جامعة عين شمس١

زميل بمركز علاج التسمم بمستشفيات جامعة عين شمس ٢

الخلفية:تعتبر الإصابة بالمواد الحارقة ، الناجمة عن تناول المواد الكاوية، مصدر قلق صحي في جميع أنحاء العالم بسبب معدلات المرض والوفيات العالية التى ترافقها.

الهدف: تهدف الدراسة الحالية إلى التحقق من الدور المحتمل لمستويات دلائل الالتهاب وهي الكورتيزول والالفا وان أنتيتريبسين والبروتين التفاعلي سي في تحديد شده الإصابة بالمواد الكاوية .

الطريقة: أجريت هذه الدراسة المستقبلية من خلال جمع البيانات الديموغرافية والسريرية وعينات الدم من 30 مريضاً تناولوا مواد كاوية و تم إدخالهم إلى مركز علاج التسمم بمستشفيات جامعة عين شمس. تم تحليل صوره الدم ومستوي دلالات الالتهاب بعد مرور ٢٤ ساعة و٧٢ ساعة من ابتلاع المواد الكاوية. كما تمت متابعة المرضى في العيادة الخارجية لمدة ثلاثة أسابيع لبيان حدوث ضيق بالجهاز الهضمي .

النتائج: كان المرضى الذين خضعوا للدراسة 13 أنثى (43.3٪) و 17 ذكر (56.7٪) وكان متوسط أعمارهم 2.7 ± 1.26 سنة. تم إدخال عشرين مريضاً إلى القسم الداخلى وتم إدخال عشرة مرضى إلى وحدة الرعاية المركزة. كان وجود قيء دموي وضيق تنفسي وحمضية بالدم عند الدخول وحدوث ضيق بالجهاز الهضمي وطول مده الاقامه بالمستشفى أعلى بشكل ملحوظ في مجموعة مرضى الرعاية المركزة عنه فى مجموعة مرضى القسم الداخلى . وكان مستوي البروتين التفاعلي سي والالفا وان أنتيتريبسين عالي بشكل ملحوظ في مجموعه مرضي الرعاية المركزة وكانت المستويات العاليه لكليهما مرتبطة بشكل طردى مع طول مده الاقامة بالمستشفي . وقد ارتبط مستوي الالفا وان أنتيتريبسين فوق 179 بعد 24 ساعه بشكل كبير بحدوث ضيق بالجهاز الهضمي .

الاستنتاج: تقدم هذه الدراسه ادلة تدعم الدور المحتمل لبروتين سي التفاعلي والالفا وان أنتيتريبسين كمؤشرات حيوية موثوقه للتنبوء بشده ونتائج تناول المواد الكاوية. علاوه على ذلك تعتبر قيمه مستوى الالفا وان أنتيتريبسين فى الدم التى تزيد عن 179 قيمة فاصلة تؤخذ فى الاعتبار للتنبؤ بحدوث ضيق فى الجهازالهضمي لدى المرضي الذين تناولوا المواد الكاوية ومن ثم توجية العلاج لتحقيق نتائج افضل للمرضى

التوصيات:توصي الدراسة الحاليه بتكثيف المبادارات الموجهه نحو الوقاية من الاصابات الكاوية لانها تظل افضل نهج لتقليل المرض والوفيات الناجمة عن تناول المواد الكاوية.