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Study of serum creatine phosphokinase (CPK) as a prognostic indicator in patients with organophosphorus compound poisoning

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***Abstract*---**Organophosphorus (OP) is an easily accessible pesticide which has a high morbidity and mortality on human exposure. Serum cholinesterase (SChE) is usually used for assessing the severity of poisoning, in this study we assess the role of serum creatine phosphokinase (CPK) as an alternative prognostic marker. This was a single centred, hospital-based, prospective and observational study, conducted on 88 patients with a history of OP compound consumption who were admitted to the ICU of tertiary care hospital, from the time period October 2019 to March 2021. The patients were clinically categorized into mild, moderate and severe categories according to Peradeniya Organophosphorus Poisoning (POP) scale and before initiation of treatment, the samples were sent for estimation of SChE and serum CPK. Out of the 88 patients, OP poisoning was more common in the age group of 21-30 years and males had a higher incidence. Chlorpyriphos (62.5%) was the most common compound. A higher POP score, marked reduction in SChE levels, and increased

serum CPK levels were observed to have increased the duration of hospital stay, increased the severity of poisoning, increased the need for ventilator support and also increased the mortality. POP score, SChE and serum CPK on admission were reliable predictors of prognosis and outcome in patients with OP poisoning, of which serum CPK levels was found to be a cheap and better predictor.

Keywords---organophosphorous (OP), peradeniya organophosphorus poisoning (POP), serum cholinesterase (SChE), serum creatine phosphokinase (CPK), survived without intubation (SWOI), survived with intubation (SWI).

Introduction

Accidental and intentional poisonings or drug overdoses constitute a significant source of aggregate morbidity, mortality, and health care expenditure worldwide.[1] Organophosphates (OP) are organic derivatives of phosphorus used as insecticides, medications, and nerve agents.[2] Tetraethyl pyrophosphate (TEPP) was synthesized in 1854 as the first OP cholinesterase inhibitor.[3] Worldwide, an estimated 3,000,000 people are exposed to organophosphate agents each year, with up to 300,000 fatalities.[4]

Toxicity generally results from accidental or intentional ingestion or exposure to agricultural pesticides. [5] Other potential causes of organophosphate toxicity include ingestion of contaminated fruit, flour, or cooking oil and wearing contaminated clothing. Easy accessibility and lenient rules and regulations regarding sales make organophosphorus compounds one of the most commonly used means for deliberate self-harm.

These compounds act by inhibiting the enzyme acetylcholinesterase (AChE), which results in an overabundance of acetylcholine at the neuronal synapses and the neuromuscular junction leading to a wide range of symptoms caused by muscarinic nicotinic and Central Nervous System (CNS) effects.[6] After ingestion, symptoms usually appear within 30-90 minutes and a maximum of 24hrs in case of compounds that are highly lipophilic and which require metabolic bioactivation.[7] Based on these signs and symptoms, Senanayake N proposed Peradeniya Organophosphorus Poisoning (POP) scale for grading the severity.[8] (Table).

Table 1: Peradeniya Organophosphorus Poisoning (POP) scale

Parameter	**Criteria**	**Score**
Pupil size	≥2mm	0
	<2mm	1
	Pinpoint	2
RR	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2

HR	>60/min	0
	41-60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal command	1
	No response to verbal command	2
Seizures	Absent	0
	Present	1
0-3 Mild poisoning	4-7 Moderate poisoning	8-11 Severe poisoning

Patients die mostly from respiratory failure and lung injury, although there is variability in the clinical symptoms and signs depending on the nature of compounds, amount consumed, severity, the time gap between exposure, and presentation in the hospital. Patients with acute OP poisoning are usually monitored by using serum cholinesterase (SChE) levels which are expected to fall as the severity of poisoning increases. But estimation of their levels is costly and is not regularly performed in most laboratories of our country.

There are emerging options for newer economically viable and easily quantifiable biochemical markers in relation to OP poisonings like creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and serum immunoglobulins (IgG, IgA). [9] As of today, only very few studies have shown that serum cholinesterase level and serum CPK level estimations are useful in the diagnosis of organophosphorus poisoning in the acute phase. [10] [11] [12] With this background in mind, we undertook a study to assess the role of CPK as an alternative prognostic marker and to establish a correlation between CPK levels and the severity of OP poisoning.

Material and Methodology

Aim and objectives

To study the relation of serum creatine phosphokinase (CPK) levels and serum Cholinesterase (SChE) levels with Peradeniya Organophosphorus Poisoning score (POP score) in patients with organophosphorus compound poisoning, and to predict their prognosis and outcome.

Study design

This was a single centered, hospital-based, prospective and observational study, conducted on patients with a history of organophosphorus compound consumption.

Study setting

The study was conducted on 88 patients who were admitted to the intensive care unit of tertiary care hospital, from the time period October 2019 to March 2021. The Institutional Ethical committee approval was taken (IEC protocol number: 229/2019-2020). Written and informed consent were obtained from all participants or their relatives before including them in the study.

Inclusion criteria: All patients aged more than 18 years who have been exposed to organophosphorus compound and admitted within 12 hours without any prior treatment.
Exclusion criteria: Patients with a history of myopathy, chronic renal disease, seizure disorder, ischemic heart diseases, sepsis and trauma; patients on medication like statins, fibrates, aspirin, and anticoagulants; patients receiving intramuscular injections; patients who consumed non-organophosphorus compounds were excluded from our study.

Data collection: Patients meeting the inclusion criteria underwent a detailed clinical examination with particular reference to vital signs, assessment of central nervous system, respiratory system and cardiovascular system. This examination was carried out at the initial presentation in the emergency room and the cases were followed up during their ward/ICU stay. Peradeniya organophosphorus scale was applied to each patient at the time of admission and the severity of the poisoning was graded as mild [score 0-3], moderate [score 4-7], severe [score 8-11].[8] Before initiation of treatment, the samples were sent for estimation of SChE and serum CPK. LiquiCHECK™ kit was used for in vitro quantitative determination of SChE using the new DKGC (Deutsche Gesellschaft Fur Klinische Chemie) method with a reference range of 4620 – 11200 IU/L. CK (creatine kinase) kit was used for in vitro quantitative determination of Creatine phosphokinase activity in the serum using the modified IFCC (International Federation of Clinical Chemistry) method with a reference range of 60 and 400 IU/L. Both these biochemical parameters were analyzed in a semi-automated Erba Chem 5® Plus V2 analyzer by Transania.

Statistical analysis

A predesigned study proforma sheet was used to collect the data and was entered in Microsoft Excel. Appropriate statistical tests were applied using Statistical Package for Social Sciences (SPSS) software version 27 for analysis. Qualitative data was represented in the form of frequency and percentage. Quantitative data was represented using Mean with Standard Deviation (SD) and Median with interquartile range (IQR). Chi-square test and 't' test was used and a 'p' value <0.05 was taken as statistically significant. Correlation of various parameters with POP score, SChE, serum CPK were made with Pearson's and Spearman's

rank correlation. The correlation coefficient, ('r' value) of 0.8-1.00, 0.4-0.79 and 0-0.39 were considered as strong correlation, moderate correlation and weak correlation, respectively. The area under receiver operating characteristic curve (AUROC) for POP score, SChE, and serum CPK was calculated and a value closer to 1.0 was considered significant.

Results

Demography

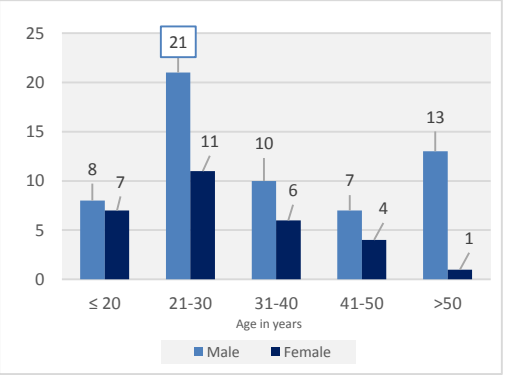

Figure 1: Age and gender distribution

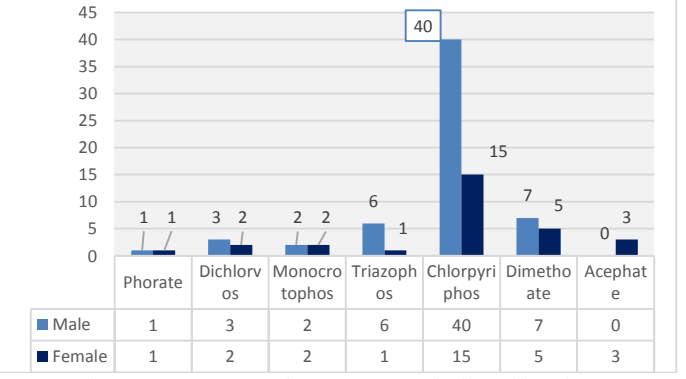

Figure 2: Type of Compound distribution

A total of 88 patients were taken in the study. The majority of the patients were in the age group of 21- 30 years (36.4%), followed by 31-40 years (18.2%). The mean age of the study population was 33.86 ± 14.46 years, with a minimum age of 18 years and maximum age of 78 years. Amongst the 88 study subjects, 59 (67%) were males and 29 (33%) were females (Figure 1).A majority of 67 (76.1%) patients did not have any comorbidity, and 21 (23.9%) had comorbidities. Hypertension was found to be the commoner comorbidity with a prevalence of 10.2%, followed by type 2 diabetes mellitus with a prevalence of 8 %. Chlorpyriphos (62.5%) was the most common compound, followed by dimethoate (13.6%) (Figure 2). The most common manner of poisoning was suicidal (100%), and the exposure route was oral. In the present study, 74 (84%) patients had vomiting as the most common

symptom, 69 (78.4%) patients had miosis, 53 (60.2%) patients had bradycardia, 68 (77.3%) had tachypnoea, 38 (43.2%) had fasciculations, 37 (42%) had altered sensorium and 5 (5.7%) had seizures.

Outcome

Of the total 88 patients admitted, 76 (86.36%) survived, and 12 (13.6%) patients succumbed, and the case fatality rate in the population was 13.63%. Amongst the survivors, 28 (31.8%) survived without respiratory failure, and 48 (54.5%) had respiratory failure and survived with mechanical ventilation. (Figure 3) The mean age of the group of survivors group was 32.18 ± 14.26, and the mean age in the group of non-survivors was 44.50 ± 11.18. The mean age in the group of non-survivors is higher than that of survivors. Out of the 12 non-survivors, 10 were males, and 2 were females. The fatality rate in males was 16.9 % as compared to 6.9 % in females. It was observed that the case fatality rate was 28.6% in patients with comorbidities compared to 9 % case fatality amongst the patients without any comorbidity. Monocrotophos, triazophos, and acephate had 0% case fatalities in contrast with phorate which had 100 % case fatalities. Dichlorvos, chlorpyriphos, and dimethoate had a case fatality rate of 40%, 10.9%, and 16.7%, respectively.

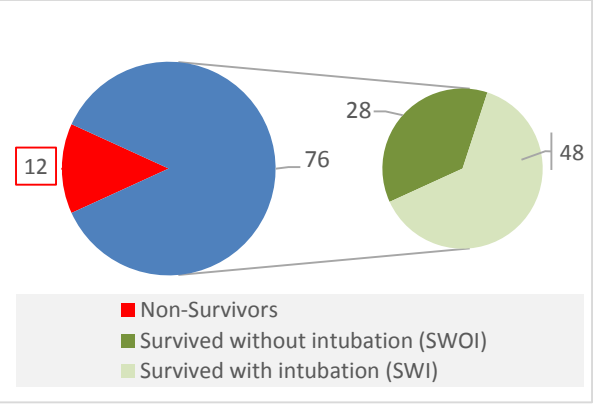

Figure 3: Outcome distribution

POP and severity

A majority of 18 (20.5%) patients had a Peradeniya Organophosphorus Poisoning (POP) score of 2, followed by 15 (17%) patients who had a POP score of 4. None had a POP score of 11. The maximum value of the POP score observed in the patients was 10, and the minimum was 0. The mean POP score observed was 4.09 ± 2.53.

According to the POP score, patients were categorized into mild, moderate, and severe poisoning categories. A majority of 40 (45.5%) patients belonged to mild poisoning, 35 (39.8%) patients belonged to moderate poisoning, and 13 (14.8%) patients belonged to severe poisoning. As the severity of the poisoning increased, the mortality also increased. The case fatality rate was 0%, 11.4%, and 61.5% among the mild, moderate and severe poisoning, respectively and the difference

between the case fatality rate is statistically significant. (DF = 2; X^2 = 31.790; 'p' value < 0.001). (Figure 4)

The mean POP score was 3.55 ± 2.175 among the survivors and 7.50 ± 1.931 in the group of non-survivors. Among the survivors, patients who did not have respiratory failure had a mean POP score of 2 ± 1.122, and patients who had respiratory failure and survived with ventilatory support had 4.46 ± 2.133 as mean POP score. As the POP score increased, the severity and mortality also increased. The difference between the mean POP score in the 3 groups is statistically significant. (DF = 2; 'p' value = 0.000). (Figure 5)

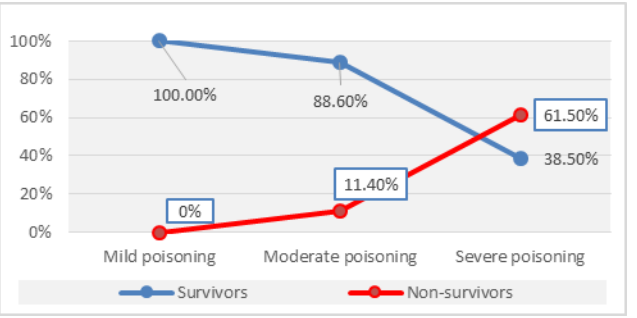

Figure 4: POP severity and case fatalities

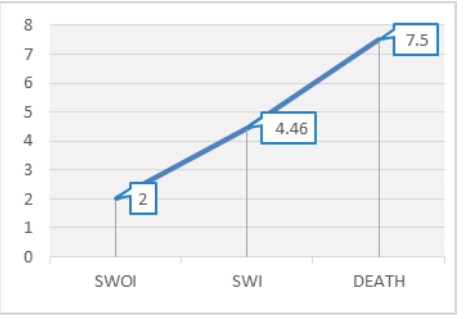

Figure 5: Mean POP score and outcome

There was a moderate positive correlation between the POP score and the outcome ('r' = 692; 'p' value < 0.001). The AUROC for the POP score for predicting mortality was 0.901. The POP score of ≥6 had had a sensitivity of 75% and specificity of 82.89%.

Serum cholinesterase (SChE)

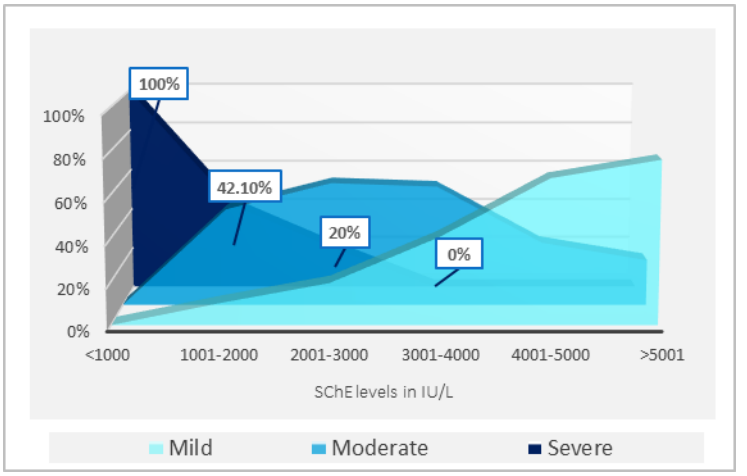

Figure 6: SChE level distribution according to POP severity

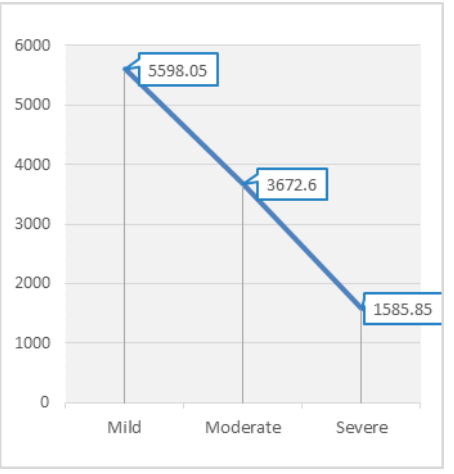

Figure 7: Mean SChE and Severity

A majority of 27 (30.7%) patients had serum cholinesterase (SChE) levels of more than 5001 IU/L of which 21 (77.8%) belonged to the mild category, 6 (22.2%) belonged to moderate poisoning. Patients with SChE above 3001 IU/L had mild to moderate severity of poisoning only, in contrast to patients with SChE levels below 3000 IU/L who had mild, moderate, and severe type of poisoning. There were 2 (100%) patients who had SChE levels below 1000 IU/L

and had severe poisoning according to POP score severity (Figure 6). The mean SChE was 4239.53 ± 2706.21. The mean SChE level was 5598.05 ± 2617.72

IU/L, 3672.6 ± 2366.99 IU/L and 1585.85 ± 483.10 IU/L in the mild, moderate and severe group respectively. As the severity of poisoning increased, the SChE levels decreased ('p' value <0.001) (Figure 7). There was a moderate negative correlation between SChE levels and the severity of poisoning ('r' = -609; 'p' value < 0.001).

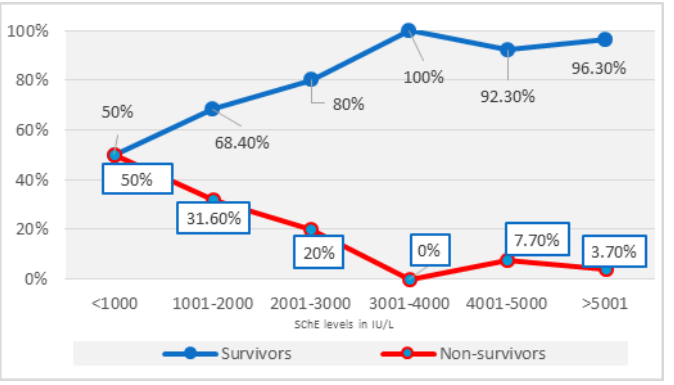

Figure 8: SChE levels and case fatalities

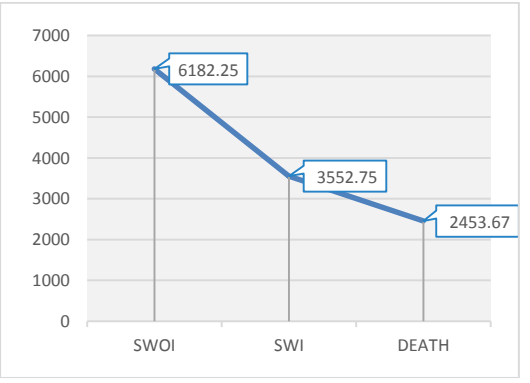

Figure 9: Mean SChE level and outcome

SChE levels below 1000 IU/L had 50% case fatalities, and levels above 5000 IU/L had 3.7% case fatalities. As the SChE levels decreased, the case fatalities increased. The difference between the case fatality rate is statistically significant. (DF = 5; X^2 = 12.502; 'p' value = 0.029) (Figure 8). The mean SChE level was 4521 ± 2717.01 IU/L in the group of survivors and 2453.67 ± 1887.27IU/L in the non-survivors. Amongst the survivors, 6182.25 ± 2433.137 IU/L was the mean SChE levels in patients who did not have respiratory failure, and 3552.75 ± 2403.645 IU/L was the mean SChE levels in patients who had respiratory failure and survived with the help of mechanical ventilation ('p' value <0 0.001) (Figure 9). The area under the curve of the receiver operator characteristic (AUROC) of serum cholinesterase with survivability as the outcome was 0.764 (95% CI: 0.616 - 0.912, 'P' value = 0.003) with a sensitivity of 72.4% and a specificity of 83.3% when the cut-off value was 2428 IU/L.

Serum creatine phosphokinase (CPK)

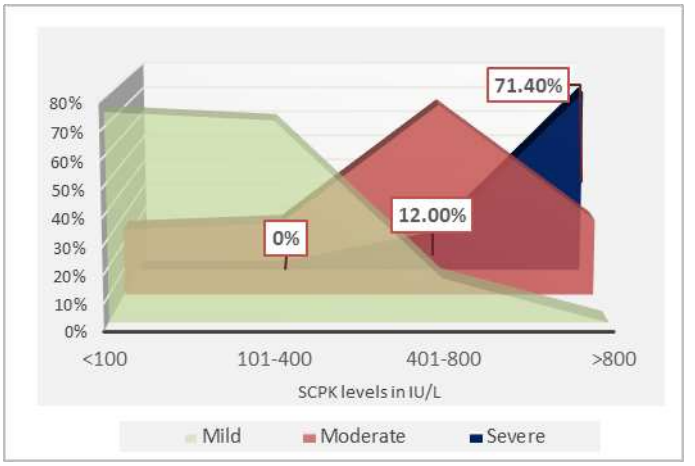

Figure 10: Serum CPK level distribution according to POP severity

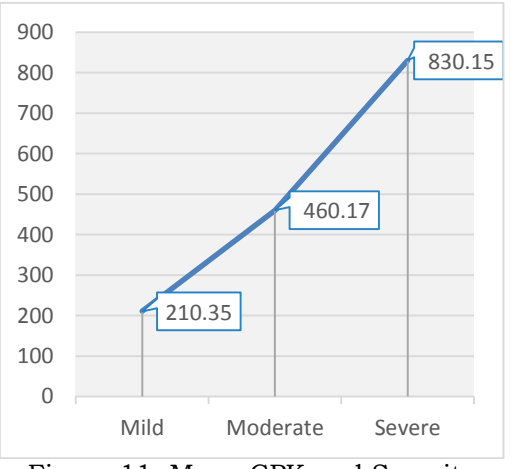

Figure 11: Mean CPK and Severity

A majority of 33 (37.5%) patients had their serum creatine phosphokinase (CPK) levels between 101-400 IU/L. 11 (12.5%) patients had their serum CPK levels more than 800 IU/L, of which 8 (72.7%) patients had severe poisoning, and 3 (27.3%) patients had moderate poisoning, and none had mild poisoning. Out of the 16 (18.2%) patients who had serum CPK levels below 100 IU/L, 12 (75%) patients had mild poisoning, and 4 (25 %) patients had moderate poisoning, and none had severe poisoning. Patients who had serum CPK levels below 400 IU/L did not have severe poisoning (X^2 = 55.648; DF =6; 'p' value < 0.001) (Figure 10). The mean serum CPK level was 401.27 ± 298.28 IU/L. The mean serum CPK level was 210.35 ± 146.63 IU/L, 460.17 ± 245.59 IU/L and 830.15 ± 270.89 IU/L in the mild, moderate and severe group respectively. As the severity of poisoning increased, the serum CPK levels increased ('p' value < 0.001) (Figure 11). There was a moderate positive correlation between serum CPK levels and the severity of poisoning ('r' = 657; 'p' value < 0.001).

Serum CPK levels below 100 IU/L had 0% case fatalities, and serum CPK levels above 800 IU/L had 63.60% case fatalities. As the serum CPK levels increased, the case fatalities increased. The difference between the case fatality rate is statistically significant (DF = 3; X^2 = 29.039; 'p' value < 0.001) (Figure 12). The mean serum CPK level was 343.86 ± 260.690 IU/L in the group of survivors and 764.92 ± 270.743 IU/L in the non-survivors. Amongst the survivors, 189.25 ± 136.152 IU/L was the mean serum CPK levels in patients who did not have respiratory failure, and 434.04 ± 274.317IU/L was the mean serum CPK levels in patients who had respiratory failure and survived with the help of mechanical ventilation ('p' value < 0.001). There was a moderate positive correlation between serum CPK levels and the outcome ('r' = 598; 'p' value < 0.001) (Figure 13).

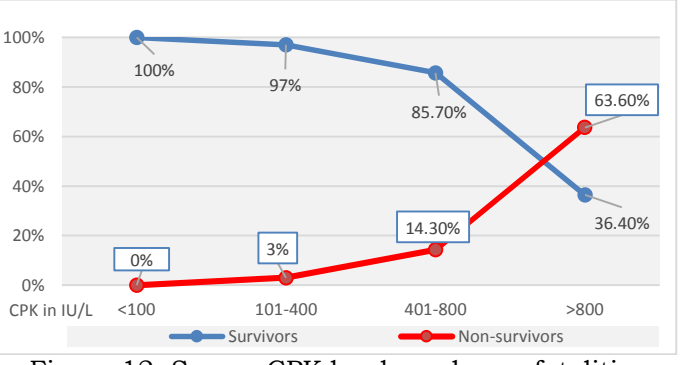

Figure 12: Serum CPK levels and case fatalities

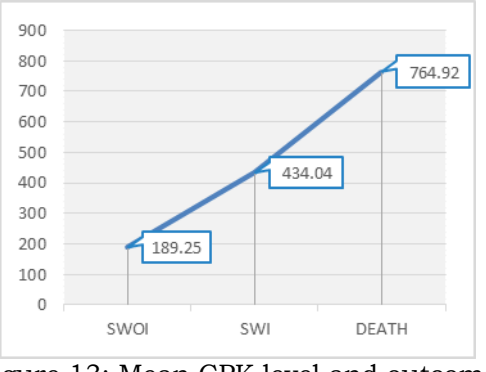

Figure 13: Mean CPK level and outcome

The AUROC for the serum CPK for predicting mortality was 0.863863 (95% CI: 0.767 - 0.959, 'p' value < 0.0001). The serum CPK level of 551 IU/L had a sensitivity of 75%and specificity of 77.6%.

POP score, SChE and serum CPK levels with outcome

As the POP score increased, the case fatality also increased. The case fatality rate was 0%,11.4%, and 61.5% among the POP score groups of 0-3, 4-7 and 8-11, respectively. The difference between the case fatality rate is statistically significant. (DF = 2; X^2 = 31.790; 'p' value < 0.001). Decremental levels of SChE levels had increasing mortality The case fatality rate was 27.8%,2.7%, and 6.7%

among the SChE level groups of <3000 IU/L, 3001-6999 IU/L and ≥7000 IU/L, respectively. The difference between the case fatality rate is statistically significant. (DF = 2; X^2 = 10.48; 'p' value = 0.005). Incremental levels of serum CPK had increased case fatality. The case fatality rate was 0%,10.4%, and 63.6% among the serum CPK level groups of <200 IU/L, 200-799 IU/L and ≥800 IU/L, respectively. The difference between the case fatality rate is statistically significant. (DF = 2; X^2 = 28.352; 'p' value < 0.001).

On comparing the groups of patients with POP score of 8-11, group of patients with SChE levels of <3000 IU/L and group of patients with serum CPK ≥800 IU/L, the case fatalities were 61.5 %, 27.8% and 63.6%, respectively. The difference between them was statistically significant. (DF = 2; X^2 = 28.352; 'p' value = 0.028) (Table 2) (Figure 14).

Table 2: POP, SChE, CPK with outcome

Parameter		Survivors (n=76)	Non-Survivors (n=12)	Total (n=88)	'p' value
POP Score	0-3	40 (100%)	0 (0%)	40 (45.5%)	<0.001
	4-7	31 (88.6%)	4 (11.4%)	35 (39.8%)	
	8-11	5 (38.5%)	8 (61.5%)	13 (14.8%)	
SChE (IU/L)	<3000	26 (72.2%)	10 (27.8%)	36 (40.9%)	0.005
	3000-6999	36 (97.3%)	1 (2.7%)	37 (42%)	
	≥ 7000	14 (93.3%)	1 (6.7%)	15 (17%)	
CPK (IU/L)	<200	29 (100%)	0 (0%)	29 (33%)	<0.001
	200-799	43 (89.6%)	5 (10.4%)	48 (54.5%)	
	≥800	4 (36.4%)	7 (63.6%)	11 (12.5%)	
POP score (8-11), SChE levels of <3000 IU/L and serum CPK ≥800 IU/L					0.028

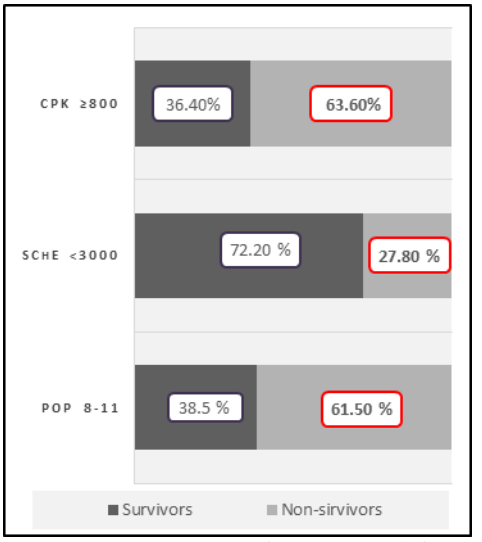

Figure 14: Serum CPK, SChE, POP with outcome

Discussion

In the present study of 88 patients, the majority of the people were in the age group of 21-30 years (36.4%) followed by 31-40 years (18.2%) with a mean age of 33.86 ± 14.46 years. The distribution according to the gender showed that 59 (67%) were males and 29 (33%) were females. This finding was similar to a study conducted by *Kumar A et al*, *Raghu G et al*, *Lokesh et al* and *Banashankari S Kollur et al* where the majority of the patients belonged to the age group of 20-30 years with male predominance.[13],[17],[18] [19] This is in contrast to the studies conducted by *Sen R et al* and *Narmeen A et al* who had female preponderance. [14],[16] The preponderance in young adults reflects the prevalent emotional conflicts in this age group. Male predominance is probably due to the high suicidal rates compared to females.[20]

Organophosphorus Compound

In our study, the most common compound was chlorpyriphos (62.5%), followed by dimethoate (13.6%) and triazophos (8%). Phorate (2.3%) was the least common compound. This is similar to the study conducted by *Mural et al* and *Das P et al* who had chlorpyriphos as the most common compound.[15], [21] In contrast to this *Lokesh et al* had dichlorvos, *Banashankari S Kollur et al* had malathion and *Subathra.C et al* had monocrotophos as the most common compound. [18], [19], [22] 100% of the cases were suicidal, and the exposure route was oral. *Narmeen A et al* reported 56.7% suicidal and 43.3% accidental exposure with 73.3% through oral route, [16] which was in contrast to a study conducted by *Weissmann-Brenner et al* which had 64% accidental and 36% suicidal exposure with 67% exposed orally. [23] Monocrotophos, triazophos, and acephate had 0% case fatalities in contrast with phorate which had 100 % case fatalities.

Comorbidities

In the present study, a majority of 67 (76.1%) patients did not have any comorbidity. 10.2% of patients had hypertension, 8% had type 2 diabetes mellitus, 3.4% had chronic obstructive pulmonary disorder, 1.1% had major depressive disorder, and 1.1% had HBsAg positive status.

Clinical features

In the present study, 74 (84%) patients had vomiting as the most common symptom. 69 (78.4%) patients had miosis, 53 (60.2%) patients had bradycardia, 68 (77.3%) had tachypnoea, 38 (43.2%) had fasciculations, 37 (42%) had altered sensorium, 5 (5.7%) had seizures. This was similar to the study conducted by *Bhattacharya K et al* and *Virupakshappa V et al.* [9],[26]

Outcome

In the present study, out of the total 88 patients, 76 (88.4%) patients were survivors, of which 28 (31.8%) patients did not have respiratory failure and 48 (54.5%) patients had respiratory failure and survived with mechanical ventilatory support. 12 (13.6 %) patients were non-survivors. A majority of the patients were survivors with respiratory failure, which was in contrast to the studies conducted by *Kumar A et al, Dayanand Raddi et al* and *Banashankari S Kollur et al* which had a majority of patients belonging to survivors without respiratory failure. [13], [24], [19] A study conducted by *Das P et al* and *Siddraj Wali et al* also included survivors and non-survivors from intermediate syndrome. [21], [27]

- The mean age of the group of survivors group was 32.18 ± 14.26, and the mean age in the group of non-survivors was 44.50 ± 11.18. The mean age in the group of non-survivors is higher than that of survivors.
- Out of the 12 non-survivors, 10 were males, and 2 were females. The fatality rate in males was 16.9 % as compared to 6.9 % in females.
- It was observed that the case fatality rate was 28.6% in patients with comorbidities compared to 9 % case fatality amongst the patients without any comorbidity.

Severity of poisoning based on Peradeniya Organophosphorus Poisoning scale

Peradeniya Organophosphorus Poisoning scale was used to assess the severity of poisoning at the time of admission. 45.5% of the patients had mild poisoning, 39.8 % patients had moderate poisoning, and 14.8% had severe poisoning according to POP score. Similar findings were found in the studies conducted by *Kumar A et al*, *Mural et al*, *Raghu G et al* and *Narmeen A et al.*.[13],[15],[17],[16] The study conducted by *Bhattacharya K et al* and *Sen R et al* had a majority of the patients belonging to moderate severity.[9] [14] *Banashankari S Kollur et al* [19] and *Dayanand Raddi et al* [24] used Modified Drieshbch's criteria [25] for grading the severity of poisoning.

As the severity of the poisoning increased, the mortality also increased. The case fatality rate was 0%,11.4% and 61.5% among the mild, moderate and severe poisoning, respectively. The mean POP score in the SWOI (Survived Without Intubation/respiratory failure) group was 2 ± 1.122, SWI (Survived with intubation/ with respiratory failure) group was 4.46 ± 2.133 and the non-survivors group was 7.50 ± 1.931. According to Spearman's rank correlation coefficient, the association between the POP score and the outcome had a positive correlation ('r' = 692'p' value < 0.001). The AUROC for the POP score for predicting mortality was 0.901. The POP score of ≥6 had had a sensitivity of 75% and specificity of 82.89%.

Serum cholinesterase

a. Serum cholinesterase and severity of poisoning
   It was found that the mean serum cholinesterase level was 5598.05 ± 2617.72 IU/L in the mild group, 3672.6 ± 2366.99 IU/L in the moderate group and 1585.85 ± 483.10 IU/L in the severe group. As the serum cholinesterase levels decreased, the severity of poisoning increased. This was similar to the studies conducted by *Mural et al*, *Narmeen A et al* and *Bhattacharya K et al.* [15],[16],[9] The association between serum cholinesterase levels and the severity of poisoning had a moderate negative correlation according to Spearman's rank correlation coefficient ('r' = -609; 'p' value < 0.001). This was similar to the study conducted by *Sen R et al* (r' =-0.267), but this had a weak negative correlation. [14]
b. Serum cholinesterase and outcome
   The mean serum cholinesterase level among the survivors was 4521 ± 2717.01 IU/L, of which 6182.25 ± 2433.137 IU/L was the mean serum cholinesterase level among survivors without respiratory failure and 3552.75 ± 2403.645 IU/L was the mean serum cholinesterase level among and survivors with respiratory failure. The mean serum cholinesterase level among the non-survivor was 2453.67 ± 1887.277 IU/L. The non-survivors had lower levels of serum cholinesterase levels compared to the survivors. As the serum cholinesterase levels decreased, the mortality increased. This was similar to the studies conducted by *Sen R et al* where the mean SChE level among survivors was 1593.23 ± 1539.2 IU/L, and the non-survivors was 802.80 ± 652.97 IU/L. [14] Similar results were found in a study conducted by *Senthilnathan N K et al* with mean SChE levels of 2357.34 ± 2242.477IU/L and 821 ± 399 IU/L among survivors and non-survivors, respectively. [28]

The association between serum cholinesterase levels and the outcome had a negative correlation according to Spearman's rank correlation coefficient. ('r' = -569; 'p' value < 0.001) The area under the curve of the receiver operator characteristic (AUROC) of serum cholinesterase for predicting the outcome was 0.764 (95% CI: 0.616 - 0.912, 'P' value = 0.003) with a sensitivity of 72.4% and a specificity of 83.3% when the cut-off value was 2428 IU/L. This was similar to the study conducted by *Narmeen A et al* where the AUROC was 0.78 and considered the cut-off value of ≤ 2895 IU/L [16]

Serum creatine phosphokinase

When the serum creatine phosphokinase levels at the time of admission were analyzed, the mean CPK levels was 401.27 ± 298.28 IU/L, which had similar values of 464.64 ± 381.97 IU/L in the study conducted by *Subathra.C et al.* [22]

a. Serum creatine phosphokinase and severity of poisoning
The mean serum CPK level was 210.35 ± 146.63 IU/L in the mild group, 460.17 ± 245.59 IU/L in the moderate group, and 830.15 ± 270.89 IU/L in the severe group. As the serum CPK levels increased, the severity of poisoning also increased. This was similar to the study conducted by *Sen R et al* where mean CPK levels were 449.65 IU/L, 768.2 IU/L, 1324.74 IU/L in mild, moderate and severe category respectively. [14] *Narmeen A et al* also had similar results but had much lower mean CPK levels in the POP severity groups (89.1 IU/L, 273 IU/L, 688.8 IU/L in mild, moderate and severe category respectively). [16] Our study was closely similar to *Bhattacharya K et al* where 273.53 IU/L, 456.06 IU/L, 1032.57 IU/L, was the mean CPK levels in the mild, moderate and severe group, respectively. [9] The association between creatine phosphokinase levels and the severity of poisoning had a moderate positive correlation according to Spearman's rank correlation coefficient ('r' = 657; 'p' value < 0.001). The study conducted by *Sen R et al* had a similar positive correlation (r' = 625). [14] But the study conducted by *Das P et al* had a strong positive correlation (r' = 0.847). His study also showed that serum CPK levels had a positive correlation with atropine dosage.[21]

b. Serum creatine phosphokinase and outcome
In this present study, the mean CPK level among the survivors was 343.86 ± 260.690 IU/L, of which 189.25 ± 136.152 IU/L was the mean CPK level among survivors without respiratory failure and 434.04 ± 274.31 IU/L was the mean CPK level among and survivors with respiratory failure. The mean creatine phosphokinase level among the non-survivor was 764.92 ± 270.74 IU/L. The non-survivors had higher levels of serum CPK levels compared to the survivors. As the serum CPK levels increased, the mortality increased. These findings were almost similar to the study conducted by *Mural et al*, where the mean serum CPK levels was 183.1 ± 65.9 IU/L and 489.9 ± 76 IU/L among the survivors without intubation and the survivors with intubation, respectively. The mean serum CPK level was 2139.8 ± 149.1 IU/L among the non-survivors. [15]
This was similar to the studies conducted by *Sen R et al* where the mean CPK level among survivors was 698.58 ± 486.48 IU/L, and the non-survivors was 1277.81 ± 645.23 IU/L.[14] Similar results were found in a study conducted by *Senthilnathan N K et al* with mean serum CPK levels of 444.76 ± 621IU/L and 1296.24 ± 1120 IU/L among survivors and non-survivors, respectively. [28]
The study by *Raghu G et al* included respiratory failure as an outcome. Respiratory failure was present in 50.7% of patients with elevated CPK levels, and no patient had respiratory failure with normal CPK levels. [17] *Das P et al* showed a significant relation between serum CPK levels and ventilator requirement, group of patients with mean CPK level of 848.72 ±

320.1 IU/L required ventilator support, and a group of patients with mean CPK levels of 420.79 ± 456.72 did not require ventilator support. [21]

The association between serum creatine phosphokinase levels and the outcome had a positive correlation according to Spearman's rank correlation coefficient. ('r' = 598; 'p' value < 0.001)

The area under the curve of the receiver operator characteristic (AUROC) of serum creatine phosphokinase for predicting the outcome was 0.863 (95% CI: 0.767 - 0.959, 'P' value < 0.0001) with a sensitivity of 75% and a specificity of 77.6% when the cut-off value was 551 IU/L. This was similar to the study conducted by *Narmeen A et al* where the AUROC was 0.77 and considered the cut-off value of ≥ 146.5 IU/L. [16] Receiver operator characteristic (ROC) curve was done to assess if the serum CPK levels at the time of admission could be used as an alternative biomarker for serum cholinesterase levels in predicting the severity and prognosis in acute organophosphorus poisoning.

Correlations of CPK (Figure 13)

a. Association of serum CPK and POP scale severity

In this present study, there was a moderate positive correlation between serum CPK levels and the severity of poisoning ('r' = 657; 'p' value < 0.001). This was similar to the study conducted by *Narmeen A et al* ('r' = 840; 'p' value < 0.001) but had a strong positive correlation.[16]

b. Association of serum CPK and serum cholinesterase levels

There is a moderate negative correlation between Serum CPK and serum cholinesterase levels ('r' = -0.398; 'p' value < 0.001). This was similar to the study conducted by *Narmeen A et al* ('r' = -810; 'p' value < 0.001) but had a strong negative correlation. [16]

c. Serum CPK levels and other associations

- There is a weak positive correlation between serum CPK levels and age ('r' = 0.250; 'p' value = 0.019).
- There is a moderate negative correlation between serum CPK levels and heart rate ('r' = -0.536; 'p' value = 0.019).
- There is a moderate positive correlation between serum CPK levels and respiratory rate ('r' = 0.520; 'p' value < 0.001).
- There is a weak positive correlation between serum CPK levels and duration of hospital stay ('r' = 0.135; 'p' value = 0.210).

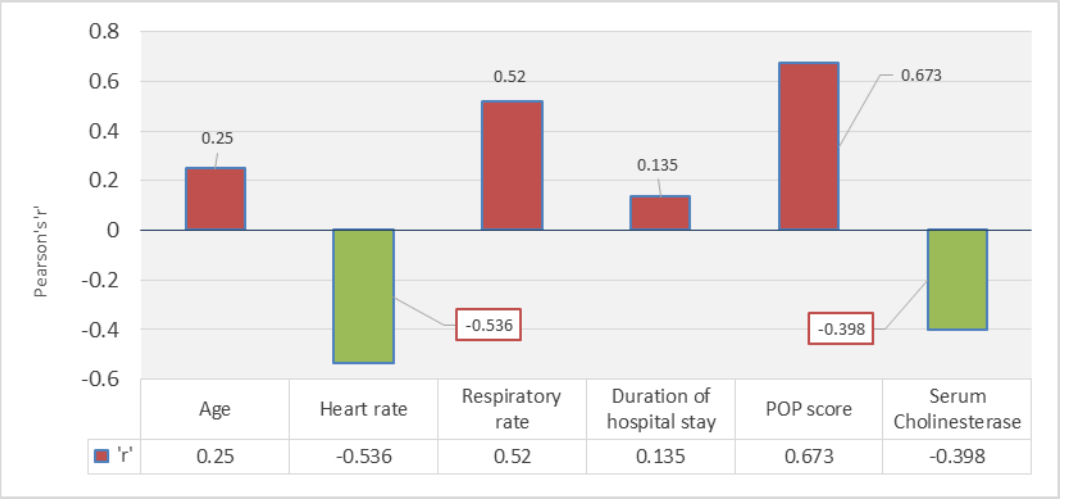

Figure 13: Serum CPK correlation with various parameters

POP score, SChE and serum CPK levels with outcome

On comparing the groups of patients with POP score of 8-11, group of patients with SChE levels of <3000 IU/L and group of patients with serum CPK ≥800 IU/L, the case fatalities were 61.5 %, 27.8% and 63.6%, respectively. The difference between them was statistically significant. (DF = 2; X^2 = 28.352; 'p' value = 0.028). Serum CPK can be used as a better biomarker to predict the prognosis and outcome in acute organophosphate compound poisoning.

Table 3: Comparison of various studies with the present study

Study	Outcome				
	Mean (IU/L)	Survivors		Non-survivors	'p' value
		Survived Without Intubation (No Respiratory failure)	Survived With Intubation (Respiratory failure)		
Present study	a) SChE	6182.25 ± 2433.137	3552.75 ± 2403.645	2453.67 ± 1887.27	<0.001
	b) CPK	189.25 ± 136.152	434.04 ± 274.31	764.92 ± 270.74	<0.001
Mural et al [15] (2017)	a) SChE	-	-	-	-
	b) CPK	183.1 ± 65.9	489.9 ± 76	2139 ± 149.1	<0.001
Sen R et al [14] (2014)	a) SChE	1593.23 ± 1539.2		802.80 ± 652.97	0.025
	b) CPK	698.58 ± 486.48		1277.81 ± 645.23	0.002
Senthilnathan N K et al [28] (2017)	a) SChE	2357.34 ± 2242.477		821 ± 399	0.000
	b) CPK	444.76 ± 621		1296.24 ± 1120	0.001

Conclusion

Organophosphorus pesticides are readily available in the market due to their wide range of applications for agriculture and domestic purposes. Organophosphorus compounds are one of the frequently consumed poisons with lethal complications such as respiratory muscle paralysis leading to respiratory failure, which requires ventilator support. Peradeniya organophosphorus poisoning (POP) score for calculation of severity of organophosphorus compound poisoning is an easy, quick and inexpensive method that can be used on all patients presenting with organophosphorus poisoning as a predictor of outcome. A higher POP score, marked reduction in serum cholinesterase levels, and increased serum creatine phosphokinase levels were observed to have increased the duration of hospital stay, increased the severity of poisoning, increased the need for ventilator support and also increased the mortality. POP score, serum cholinesterase levels, and serum creatine phosphokinase levels on admission were reliable predictors of prognosis and outcome in patients with organophosphorus poisoning, of which serum creatine phosphokinase levels was found to be a cheap and better predictor.

References

1. World Health Organization. International Programme on Chemical Safety: Poisoning Prevention and Management.
2. King AM, Aaron CK (February 2015). "Organophosphate and carbamate poisoning". Emergency Medicine Clinics of North America. 33 (1): 133–51. doi:10.1016/j.emc.2014.09.010.
3. Petroianu, Georg (2015). "History of organophosphorus cholinesterase inhibitors & reactivators". Military Medical Science Letters. 84 (4): 182–185. doi:10.31482/mmsl.2015.023.
4. Eddleston M, Phillips MR. Self poisoning with pesticides. Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford,BMJ. 2004;328(7430):42.
5. Karunarathne A, Gunnell D, Konradsen F, How many premature deaths from pesticide suicide have occurred since the agricultural Green Revolution? Clin Toxicol (Phila). 2020;58(4):227. Epub 2019 Sep 9.
6. Tafuri J, Roberts J . Organophosphate poisoning. Ann Emerg Med. 1987;16(2):193.
7. Medical Toxicology 3rded. Lippincott William and Walkins; 2004: p.236, 1477-79,1481-82.
8. Senanayake N, De Silva HJ, Karalliledde L. A scale to assess severity of organophosphorus intoxication: POP scale. Hum Exp Toxicol. 1993; 12:297-99.
9. Bhattacharyya K, Phaujdar S, Sarkar R. Serum creatine phosphokinase: a probable marker of severity in organophosphorus poisoning. Toxicol Interna. 2011;18(2):117-23.
10. Goswamy R, Chaudhuri A, Mahashur AA. Study of Respiratory Failure in Organophosphorus and Carbamate poisoning. Heart Lung. 1994;23(6):46672.
11. Aygun D. Serum Acetylcholinesterase and Prognosis of Acute Organophosphorus poisoning J Toxicol. 2002;40(7):903-10.

12. Agarwal SB, Bhatnagar VK, Agarwal A, Agarwal U, Venkaiah K, Nigam SK, et al. Impairment in clinical indices in acute organophosphate insecticide poisoning patients in India. Internet J Toxicol. 2007;4:1.
13. Kumar A et al. Creatinephosphokinase in organophosphorus poisoning. Int J Adv Med. 2017 Dec;4(6):1537-1540.
14. Sen R, Nayak J, Khadanga S. Study of serum cholinesterase, CPK and LDH as prognostic biomarkers in organophosphorus poisoning. International Journal of Medical Research and Review [Internet]. 2014 Jun 30. http://medresearch.in/index.php/IJMRR/article/view/101.
15. Raghavendra Mural, Gopal Bajaj, Denny Mammen. Study of Level of Total Serum Creatine Phosphokinase as Prognostic Indicator in Acute Organophosphorus Poisoning: A Prospective Study. International Journal of Contemporary Medical Research. ICV (2015): 77.83. SSN (Online): 2393-915X.
16. Nermeen AM, Abdelmonem G. Madboly et al.Correlation between Serum Creatine Phosphokinase and Severity of Acute Organophosphorus Poisoning.
a. IOSR Journal of Environmental Science, Toxicology and Food Technology (IOSR-JESTFT): 2013; 4(5):1829.
17. Raghu G, Ayyanagouda A. Gangannavar, Manoj Kumar B. K. tudy of serum creatinine phosphokinase and serum lactate dehydrgenase as prognostic markers in organophosphorus poisoning. International Journal of Advances in Medicine. Int J Adv Med. 2020 Jul;7(7):1125-1130.
18. Lokesh N K, Shivakumar K M, Anikethan G V. Serum creatine phosphokinase as predictor of intermediate syndrome in organophosphorus poisoning. International Journal of Contemporary Medical Research 2018;5(6):F1-F4.
19. Banashankari S Kollur, Mallanna S Mulimani, study of levels of serum creatine phosphokinase and liver enzymes as A prognostic indicators in acute organophosphorus poisoning.Int. j. clin. biomed. res. 2018;4(1):57-61.
20. Värnik, P (March 2012). "Suicide in the world". International Journal of Environmental Research and Public Health. 9 (3): 76071. doi:10.3390/ijerph9030760. PMC 3367275. PMID 22690161.
21. Das P, Bhattacharjee P, Nath BK, et al. Serum creatine phosphokinase level: As a severity marker in acute organophosphate poisoning. J. Evid. Based Med. Healthc. 2018; 5(14), 1262-1266. DOI:10.18410/jebmh/2018/261.
22. Subathra.C, S. Balasubramaniyan, I. Balaji. Creatine Phosphokinase: A Prognostic Marker in Organophosphorus Compound Poisoning. Journal of Medical Science and Clinical research. DOI: https://dx.doi.org/10.18535/jmscr/v6i10.157.
23. Weissmann-Brenner A, Aviv-Vidan A and Hourvitz A, Organophosphate poisoning: A multihospital survey. I.M.A.J., 4: 573-576 (2002).
24. Dayanand Raddi, Anikethana G V. Clinical profile of organophosphorus poisoning in a tertiary care Hospital. Indian Journal of Basic and Applied Medical Research; December 2014: P ISSN: 2250-284X , E ISSN : 2250-2858
25. Dreishbach RH. Cholinesterase inhibitor pesticides. In: Hand Book of poisoning 11 th ed. Longue medical publications. California. 1983 : 106-14.
26. Virupakshappa V, Girish I. Prognostic Significance of Creatine Phosphokinase (CPK) Levels in Assessing the Severity of Organophosphorus Poisoning Compound Poisoning. Indian Journal of Emergency Medicine.2018.

27. Siddraj Wali, Basavaraj G T. Prognostic significance of creatine phospokinase (CPK) levels in assessing the severity of organophosphorus poisoning compound poisoning. MedPulse International Journal of Medicine. September 2020; 15(3): 6468.
28. Dr.L.Alen Binny MD. "Biochemical abnormalities in OPC poisoning and its prognosticsignificance." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.7 (2017): 116-19.