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Original Article

Predictive factors for liver and kidney injury in acetaminophen poisoning: A cross-sectional study

Rokhsareh Meamar [a], *Razieh Yazdi* [b], *Awat Feizi* [c], *Melika Namvar* [d], *Seyed Ali Mirbod* [e], *Nastaran Eizadi-Mood* [f,*]

[a] *Associate Professor (Clinical Toxicology), School of Medicine, Isfahan Clinical Toxicology Research Center, Khorshid Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*
[b] *General Physician (Clinical Toxicology), Isfahan University of Medical Sciences, Isfahan, Iran*
[c] *Professor (Epidemiology & Biostatistics), School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran*
[d] *General Physician, Isfahan Clinical Toxicology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*
[e] *Emergency Medicine Specialist, Slamic Azad University, Najafabad Branch, Isfahan, Iran*
[f] *Professor (Clinical Toxicology), School of Medicine, Isfahan Clinical Toxicology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

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ABSTRACT

Background: The aim of this study was to identify predictive factors for liver and kidney injury in patients with acetaminophen (APAP) poisoning.
Method: This cross-sectional retrospective study was conducted on patients over 18 years of age admitted from January to December 2020 with APAP poisoning without prior liver or kidney issues.
Results: Out of 2878 poisoned patients admitted, 146 patients with a mean age of 27.48 ± 8.92 years had APAP poisoning. Among them, 26.7% of patients experienced kidney injury, 15.1% had elevated aspartate aminotransferase (AST) and 6.11% had elevated alanine aminotransferase (ALT) both indicating hepatic injury. The amount of APAP consumed by the patient was identified as one of the best predictive factors for hepatic injury. Specifically, for every 1-g increase in APAP consumed by the patient, the odds of increased AST were 13% (odds ratio [OR] = 1.13 95% confidence interval [CI]: 1.002-1.27], P = 0.045), the odds of increased ALT were 15% (OR = 1.15 [95% CI: 0.99-1.22], P = 0.073), and the odds of an outcome with complications increased by 12% (OR = 1.12 [95% CI: 1.01-1.25], P = 0.031). The area under the curve (AUC) showed a significant relationship between the amount of APAP and the probability of hepatic injury (ALT) (AUC: 0.689; 95% CI: 0.520-0.858) (P = 0.028). The cut-off point for predicting an increase in ALT was determined to be 8.75 g of APAP, with a sensitivity of 55.6% and specificity of 71.4%.
Conclusion: The amount of APAP ingested is a clinical tool used to predict hepatic injury resulting from acute APAP overdose in adults. The recommended cut-off point of 8.75 g of APAP can help predict an increase in ALT levels.

* *Corresponding author.*
E-mail address: izadi@med.mui.ac.ir (N. Eizadi-Mood).
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Introduction

Acetaminophen (APAP) is an antipyretic analgesic available over-the-counter. It can cause severe poisoning, leading to a significant number of emergency room visits, hospitalizations, and even death.[1,2] Annually, approximately 80,000 emergency visits and 30,000 APAP-related hospital admissions occur in the United States.[1,3]

APAP poisoning is a significant concern in Iran, as evidenced by several studies identifying it as a common cause of poisoning in the northern and eastern regions of Iran.[4,5] While most cases of APAP poisoning lead to mild liver complications, it remains a leading cause of acute liver failure. In recent years, attention has shifted to its extra-hepatic side effects, such as acute kidney injury (AKI).[6] Approximately 2% of individuals poisoned with APAP and 10% of severely poisoned patients experience AKI.[7,8]

Although the Rumack-Matthew nomogram is recommended as the gold standard for assessing the risk of hepatotoxicity, many resource-limited countries lack the necessary laboratory facilities to measure serum levels of APAP. In these cases, the reported dose of ingested paracetamol serves as the primary risk assessment tool to determine the need for N-acetylcysteine (NAC) treatment.[9–11]

The limitations of the current assessment method have promoted discussions about alternative predictors of liver injury. Numerous studies in the literature have explored potential predictors of liver injury.[12–18] Additionally, it appears that the rate of hepatotoxicity differs between Asians and Western individuals. Given these potential differences among ethnicities and variations in laboratory capabilities, as well as the role of APAP poisoning in liver and kidney injury, we conducted a cross-sectional study to investigate predictive factors for liver and kidney injury in APAP poisoning.

Material and methods

Study design and Setting: This retrospective cross-sectional study was conducted at a poisoning department of educational hospital from January to December 2020. The study was approved by the Institutional Ethics Committee. The study adhered to the Declaration of Helsinki, and all participants provided informed consent. Informed consent criteria included information disclosure patient (or surrogate), competency, and voluntary consent. To protect patient confidentiality, password-protected files were used to securely store their records.

Medical documents from the Hospital archive were used to collect patient information. The study included all adults over 18 years of age who were admitted to the referral poisoning center at Khorshid Educational Hospital, Isfahan, Iran with the discharge diagnosis code T39.1 based on the International Classification of Diseases, Tenth Revision (ICD-10). Patients with pre-existing abnormal liver and kidney tests, chronic kidney disease, chronic liver disease, hepatic encephalopathy following APAP toxicity, a history of alcohol consumption, use of other herbs/medications, and those with less than a 50% completion rate on their document or who did not complete consent forms were excluded.

Data collection: A data collection form was used to record demographic information, past medical history, physical examination findings including age, gender, marital status, physical and mental illnesses, addiction history, past drug history, self-mutilation, suicide attempts, criminal history, evidence of self-harm and injection sites, time from ingestion to hospital admission (based on patient, relative, or caregiver statements), the amount of APAP ingested at once (total APAP amount taken), and patients outcomes (recovery without complication and recovery with complications). Patients with complications were recommended to follow up with a psychiatrist, neurologist, or outpatient poisoning clinic.

Laboratory parameters, including aspartate aminotransferase (AST; IU/L), alanine aminotransferase (ALT; IU/L), and creatinine (Cr) (mg/dL), were measured within 24 h of admission using blood samples. Plasma AST and ALT were measured using the Mindray Autos Analyzer (BS800) following kit protocols.

Variables: The attending physicians diagnosed for poisoning based on patient or their relative history, clinical manifestations, serum/blood toxicological tests, and toxicology urine analysis, if necessary. The diagnosis of APAP poisoning was solely based on the patient's medical history.

Acute oral overdose was defined as total dose $\geq$150 mg/kg (approximately 7.5 g in adults) within 24 h, and the NAC regimen administered intravenously was effective in treating of APAP overdose. The NAC regimen included 150-mg/kg body weight given over 30-60 min, 50 mg/kg over 4 h, and 100 mg/kg over 16 h, with a total dose of 300 mg/kg.[20]

Patients were categorized into groups; with or without liver injury and kidney injury based on plasma aminotransferase and Cr levels exceeding normal ranges.[21] Liver injury was defined as AST and ALT levels above the upper normal range of 31 IU/L for females and 37 IU/L and 41 IU/L for males, respectively (in our hospital).

Kidney injury was characterized by serum Cr levels beyond the reference level of 1.3 mg/dL for females and 1.4 mg/dL for males.

To minimize bias, strict exclusion criteria were set for patients aged over 18 years admitted for APAP poisoning, excluding those with pre-existing liver or kidney diseases, alcohol consumption history, or incomplete medical records. Clinical history and presentations were relied up for diagnosis due to regional limitations preventing plasma APAP level measurement, potentially introducing diagnostic bias. Data

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collection was standardized using archived medical records, although reliance on self-reported ingestion details may have led to information bias, mitigated through precise documentation procedures.

Statistical analysis: Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software for Windows (Version 22, SPSS Inc., Chicago, IL, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables were reported as mean (standard deviation [SD]) and as median with interquartile range (IQR) for normally and non-normally distributed data. Categorical variables were presented as number (percentage). Chi-squared or Fisher's exact tests were used for categorical data; independent samples T-test and analysis of variance (or counterpart Mann-Whitney U test and Kruskal-Wallis tests) for continuous variables were used to assess between-group differences. Spearman rank correlation coefficient or Pearson correlation as well as linear regression was used to evaluate the association of the amount of APAP taken by patients with the values of ALT and AST. Odds ratio (OR) with a 95% confidence interval (CI) was obtained by binary logistic regression analysis to quantify the association of predictors of liver and kidney injury in poisoned patients. The predictive value of the amount of APAP taken by patients for liver injury was assessed using the receiver operating characteristic (ROC) curve. The estimated area under the curve (AUC) along with a 95% CI was determined. The maximal Youden Index was used to indicate the optimal cut-off values with the highest sensitivity and specificity. For all statistical tests, two-sided P values less than 0.05 were considered significant.

Results

In our study, a total of 146 patients were included. The mean (SD) age of the study population was 27.49 (8.93) years, with 65.8% being female. The median (IQR) time interval between ingestion and admission was 3 h (1-5 h). Of the patients, 81.5% had suicidal intent, while only two patients (1.3%) experienced accidental toxicity; 15.8% had a history of suicide (n = 23). No cases had AST and ALT levels greater than 1000, and no patients required a liver transplant. There were no deaths reported during hospitalization. Treatment with NAC was administered to 88 (41.8%) patients; 30.5% were discharged with complications, with 53.8% recommended to consult a psychiatrist, 24.6% advised to consult a toxicologist, 20% advocated to consult both, and 1.5% counseled to consult a neurologist.

Demographic and toxicological data based on liver (AST and ALT) and kidney injury (Cr) are presented in Table 1. Intentional poisoning was significantly associated with both liver injury and kidney injury (P < 0.05).

Among the 146 patients, 22 (15.1%) and 17 (11.6%) experienced liver injury based on elevated AST and ALT, respectively. Additionally, 39 (26.7%) patients experienced kidney injury. The median (IQR) quantity of ingested paracetamol was 7.74 g (3.2-9). The average amount of APAP consumed was significantly higher in patients with and without liver injury, as indicated by increased AST (P = 0.035) and ALT (P = 0.004) levels. The time from ingestion to hospital admission did not show a statistically significant association with increased levels of liver or kidney injury markers (all P values >0.05) (Table 2).

The relationship between AST and ALT levels, and reported APAP dose is shown in Fig. 1A and 1B. There was a significant positive correlation between patient-reported ingested dose and AST and ALT levels (r = 0.28; P = 0.019, r = 0.36; P = 0.003, respectively). Univariable logistic regression was applied to determine the association between the amount of APAP ingested and liver injury, as well as outcome with complications, following a paracetamol overdose (Table 3). For every 1-g increase in APAP consumed, the odds of AST elevation increased significantly by 13% (OR = 1.13 [95% CI: 1.002-1.270], P = 0.045), the odds of ALT elevation increased marginally significantly (OR = 1.10 [95% CI: 0.99-1.23], P = 0.073), and the odds of outcome with complication increased by 12% (OR = 1.12 [95% CI: 1.01-1.25], P = 0.031).

The AUC revealed a significant relationship between the amount of APAP and the probability of hepatic injury (ALT) (P = 0.028) (Fig. 2, Table 4). The sensitivity and specificity for predicting liver injury based on ALT at the threshold of 8.75 of APAP were 55.6% and 71.4% and for AST were 50 % and 73%, respectively (Fig. 2, Table 4).

Discussion

APAP overdose accounts for a significant number of emergency room visits and hospitalizations annually[1,3]. Identifying rapid prognostic indicators for APAP overdose outcomes is crucial.[22] Given the limitations of the Rumack-Matthew nomogram and limited access to serum APAP levels in resource-limited settings,[9,13] we evaluated factors associated with liver and kidney injury. However, the findings of this study demonstrate that the amount of ingested APAP is significantly associated with further liver injury. According to a recent study by Mehrpour et al., which included 30,000 cases from the National Poison Data System, elevated serum levels of liver enzymes were found to be one of the most important factors in determining the outcome of acute APAP exposure.[23]

An optimal cut-off of 8.75 g was identified to detect liver damage slightly lower than the 10-g threshold reported in a study conducted in Australia.[24] This difference could be explained by the determination of a different cut-off point for liver injury. In the western Sydney study,[24] an ALT >45 U/L was indicated for liver injury without consideration of sex differences. Paracetamol can cause severe hepatotoxicity with as little as 10 g of ingested APAP following an acute overdose.[25]

The ROC analysis of APAP in our study revealed that the cut-off points of 8.75 g of APAP for predicting an increase in ALT level had a sensitivity of 55.6% and specificity of 71.4%. Several studies have evaluated the sensitivity and specificity of the patient-reported dose of APAP taken, with treatment nomogram lines.[9,26] A study conducted in Sri Lanka found a sensitivity of 89% and a specificity of only 5% for the 150-mg/kg cut-off in predicting concentration above the nomogram line. However, this study did not identify an optimal cut-off level.[26] In a retrospective study of 784 individuals, Chomchai et al.[9] reported that the sensitivity and specificity of APAP intake above 150 mg/kg, 8 g, and 10 g were 92.6% and 55.3%,

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Table 1 – General, demographic, and toxicologic characteristics up to 24 h after admission based on liver injury or kidney injury.

		Liver injury (↑ AST)	No liver injury (↑AST)	P value	Liver injury (↑ALT)	No liver injury (↑ALT)	P value	kidney injury (↑Cr)	No kidney injury	P value
		N = 22	N = 107		N = 17	N = 111		N = 39	N = 107	
Age	Mean (SD)	28.2 (8.1)	27.10 (8.5)	0.59	26.4 (8.8)	27.65 (8.3)	0.55	28.0 (10.1)	27.29 (8.5)	0.67
Sex	Male	7 (31.8%)	35 (32.7%)	0.94	7 (41.2%)	33 (29.7%)	0.34	12 (31.6%)	37 (34.6%)	0.73
	Female	15 (68.2%)	72 (67.3%)		10 (58.8%)	78 (70.3%)		26 (68.4%)	70 (65.4%)	
Type of poisoning	Intentional	21 (95.5%)	86 (100.0%)	0.047	14 (93.3%)	94 (100.0%)	0.012	29 (93.5%)	90 (100.0%)	0.015
	Accidental	1 (4.5%)	0 (0.0%)		1 (6.7%)	0 (0.0%)		2 (6.5%)	0 (0.0%)	
Past medical history	Heart disease	0 (0%)	4 (4.4%)	0.80	0 (0%)	4 (4.2%)	0.83	1 (3.4%)	3 (3.3%)	0.26
	Lung disease	0 (0%)	1 (1.1%)		0 (0%)	1 (1.0%)		0 (0%)	1 (1.1%)	
	Other	4 (21.1%)	20 (22.0%)		2 (15.4%)	21 (21.9%)		9 (31.0%)	16 (17.4%)	
	Both	0 (0%)	2 (2.2%)		0 (0%)	2 (2.1%)		1 (3.4%)	2 (2.2%)	
	No	15 (78.9%)	64 (70.3%)		11 (84.6%)	68 (70.8%)		17 (58.6%)	70 (76.1%)	
Past drug history	Yes	5 (22.7%)	24 (24.7%)	0.84	2 (11.8%)	25 (24.8%)	0.35	6 (18.8%)	27 (26.7%)	0.36
	No	17 (77.3%)	73 (75.3%)		15 (88.2%)	76 (75.2%)		26 (81.3%)	74 (73.3%)	
Mental illness history	Yes	1 (4.5%)	9 (9.0%)	0.69	0 (0.0%)	9 (8.6%)	0.36	1 (2.9%)	9 (9.0%)	0.45
	No	21 (95.5%)	91 (91.0%)		17 (100.0%)	96 (91.4%)		34 (97.1%)	91 (91.0%)	
Criminal history	Yes	1 (4.8%)	1 (1.1%)	0.33	0 (0.0%)	2 (2.0%)	>0.99	1 (3.1%)	2 (2.1%)	1.00
	No	20 (95.2%)	93 (98.9%)		15 (100.0%)	96 (98.0%)		31 (96.9%)	93 (97.9%)	
Body evidence of self-harm	Yes	0 (0.0%)	11 (14.1%)	0.33	1 (11.1%)	9 (11.1%)	0.87	1 (5.6%)	9 (11.5%)	0.42
	No	11 (100.0%)	67 (85.9%)		8 (88.9%)	72 (88.9%)		17 (94.4%)	69 (88.5%)	
Body sign of injection site	Yes	0 (0.0%)	3 (6.5%)	>0.99	1 (11.1%)	3 (6.4%)	0.61	1 (6.3%)	3 (6.0%)	>0.99
	No	11 (100.0%)	43 (93.5%)		8 (88.9%)	44 (93.6%)		15 (93.8%)	47 (94.0%)	
NAC administration	Yes	15 (68.2%)	62 (58.5%)	0.40	13 (76.5%)	64 (57.7%)	0.14	18 (50.0%)	63 (59.4%)	0.32
	No	7 (31.8%)	44 (41.5%)		4 (23.5%)	47 (42.3%)		18 (50.0%)	43 (40.6%)	

Data are presented as mean (SD) for continuous measures and the number (%) for categorical measures. Fisher's exact or chi-squared tests were used to compare categorical variables, and continuous variables were compared with independent sample t-test. The P value less than 0.05 was considered statistically significant. Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; Cr, creatinine; SD, standard deviation.

Table 2 – Reported acetaminophen dose and time to hospital arrival in patient with and without liver or kidney Injury.

	Liver injury (↑AST)	No liver injury	P value	Liver injury (↑ALT)	No liver injury (ALT)	P value	Kidney injury	No kidney injury (↑Cr)	P value
Reported paracetamol dose	10.22 (6.39)	6.67 (4.53)	0.04	15.02 (17.62)	6.92 (4.89)	0.004	8.86 (13.16)	7.34 (5.02)	0.47
Time *	3.82 (3.67)	3.98 (4.14)	0.89	4.38 (7.34)	4.16 (4.12)	0.867	4.22 (5.07)	4.16 (4.27)	0.94

P values were obtained by independent sample t-test or Mann-Whitney U test. *Time from ingestion to hospital admission (hours) Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; Cr, creatinine.

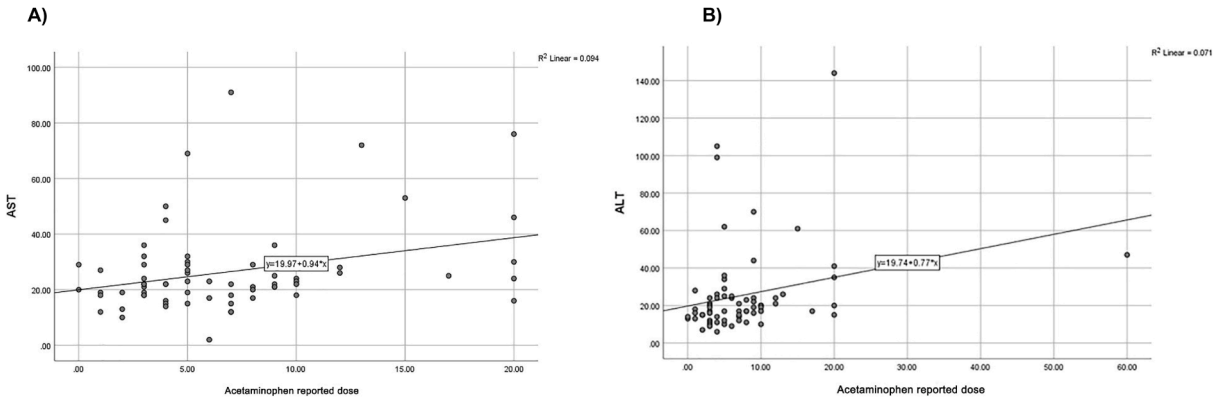

Fig. 1 – Scatter plot A and B, respectively, showing aspartate aminotransferase (AST) levels and alanine aminotransferase (ALT) levels on reported acetaminophen dose in acetaminophen-intoxicated patients.

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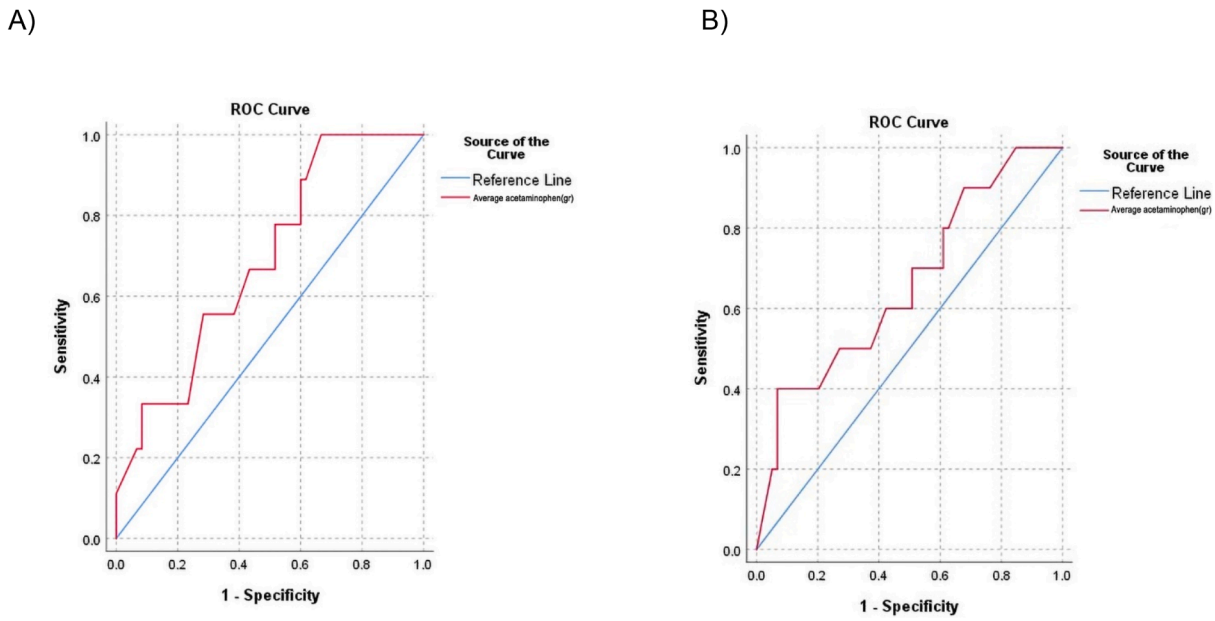

Fig. 2 – Receiver operating characteristic (ROC) curve for reported acetaminophen dose (g) in predicting liver injury (A for ALT B AST) secondary to acute acetaminophen intoxication. Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase.

Table 3 – Average of acetaminophen intake with the risk of liver injury and outcome with complication.

	Liver injury (↑AST)			Liver injury (↑ALT)			Outcome with complication		
	OR	CI (95%)	P value	OR	CI (95%)	P value	OR	CI (95%)	P value
Average acetaminophen ingested (gr)	1.13	1.002-1.277	0.045	1.10	0.991-1.225	0.073	1.12	1.010-1.245	0.031

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; CI, confidence interval; OR, odds ratio.

Table 4 – The ROC curve analysis shows that the reported acetaminophen dose can predict liver injury (ALT levels above normal) in cases of acetaminophen intoxication.

		AUC	CI (95%)	P value	Sensitivity	Specificity
Acetaminophen ingested (gr)	ALT	0.689	0.520-0.858	0.028	55.6%	71.4%
	AST	0.660	0.474-0.847	0.847	50%	73%

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

91.1% and 35.7%, and 90.6% and 39.2%, respectively, for predicting serum levels in the hepatotoxic range.

In the current study, for every 1-g increase in APAP, the odds of an increase in AST level increase by 13% (OR = 1.13). Another study similarly found a significant association between the reported APAP dose and liver injury (OR = 1.03). This association was reduced to 1.02 after adjusting for confounders.[16] Another study demonstrated that the risk of liver damage increases by 4.4 times (risk ratio = 4.4) when the consumed amount is higher than 150 mg/kg compared to consumption below 150 mg/kg.[9]

Additionally, our results revealed that the reported APAP dose had no significant association with renal injury. There was no evidence of hepatorenal syndrome in these patients, considering that their liver injury was not severe. Conversely, another study showed a significant weak correlation between the reported ingested dose and serum Cr (r = 0.138), and patients with a massive overdose were more likely to develop kidney injury.[27]

In cases of paracetamol overdose, hepatotoxicity is more common than nephrotoxicity. However, AKI can still occur even in the absence of hepatotoxicity.[28] A case series[29] reported two cases of AKI that were doubtfully induced by therapeutic-dose APAP, while a self-controlled case series study revealed no association between APAP and AKI.[30]

Unlike hepatotoxicity, the exact mechanism of nephrotoxicity in paracetamol overdose is still unclear. Studies in nonhuman animals have shown significant depletion of glutathione in the liver but not in the kidney.[31] Other animal studies suggest that paracetamol oxidation by the cytochrome P-450 system could result in tubule damage in the kidney, which may be worsened by glutathione depletion.[32]

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The potential mechanism behind paracetamol-induced nephrotoxicity could involve the activation of caspases leading to apoptosis.[31] The results indicated scarce association between APAP and AKI, presumably supporting the general physicians' impression that APAP is safer for the kidney.

In our study, 14.8% of individuals experienced liver injury based on AST levels and 11.4% experienced liver injury based on ALT levels. These rates were lower than those reported in the studies by Popiolek et al.[16] and Nuzzo et al.[17]

Furthermore, none of the patients experienced ALT and AST levels above 1000. Previous studies have also shown varied results. In other studies, the percentage of patients who experienced ALT and AST levels above 1000 was reported as 7.3% in Thailand,[9] 14% in Australia,[33] and 32% in Texas, U.S.[34] This discrepancy could be due to differences in ethnicity as previous studies reported that paracetamol overdose leads to a lower rate of hepatotoxicity in the Asian population than in Western populations. This variation may be attributed to intrinsic discrepancies in the pharmacogenetics of paracetamol metabolism, which could be a significant factor contributing to the differences in hepatotoxicity rates observed between Asians and Caucasians.[19,35]

In our study, intentional poisoning was the only demographic factors significantly associated with both liver injury and kidney injury. Severe outcomes were observed to increase with age and be lower in females in an analysis of 39,000 patients with APAP overdose.[36] This discrepancy could be explained by the smaller number of patients than in the Mehrpour et al, study.[36]

In contrast to previous studies, the time interval between ingestion and presentation did not exhibit a statistically significant difference between patients with and without liver and kidney injury.[16] This could be due to the severity of the overdose cases in our study not being as high as those in previous studies.

Our study had several limitations including its retrospective single-center design. While exclusion criteria were designed to reduce bias and control for confounding factors, they may limit the generalizability of the study's findings to wider populations. Additionally, the lack of plasma APAP–level measurements imposed a significant limitation on diagnostic precision, potentially introducing bias in evaluating the severity of poisoning. Furthermore, information bias might have arisen from the reliance on self-reported data, such as ingestion times and amounts, underscoring the inherent challenges in retrospective studies. These factors should be acknowledged as limitations in interpreting the study outcomes, and future research should address these challenges by incorporating more advanced diagnostic and data collection methods. In addition, some factors that could influence hepatotoxicity such as serum bilirubin, the timing of ingestion with food, and baseline nutritional status were not recorded in the medical report. Another crucial limitation of our study was the inability to measure serum APAP concentration in our patients. This test is crucial for evaluating the risk of liver damage and initiating NAC treatment in Western clinical practice, while we relied on reported ingested dose as an alternative indicator. The reliability of this information may be compromised by factors such as deliberate underreporting or simultaneous administration of other medications.

Conclusion

This retrospective cross-sectional study investigated probable predictors of liver and kidney injury in patients with APAP poisoning at a tertiary hospital in Iran. The study found that the amount of APAP consumed is a predictive factor for hepatic injury, but it did not show a significant relationship with renal injury. The recommended cut-off point of 8.75 g of APAP can help predict an increase in ALT levels. This finding highlights the importance of exercising caution and potentially earlier preventive intervention strategies in cases of APAP overdose. Further research is needed.

Patients/ Guardians/ Participants consent

Patients/ guardians informed consent was obtained.

Ethical clearance

Institute/hospital ethical clearance certificate was obtained.

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None.

Disclosure of competing interest

The authors have none to declare.

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