Ain Shams Journal of Forensic Medicine and Clinical Toxicology
July 2023, 41: 33-39

The Role of miRNA-122 in the Early Detection of the Degree of Liver Affection in Patients with Acute Paracetamol Toxicity Admitted to The Poison Control Center Ain Shams University Hospitals

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Abstract

Background: Paracetamol toxicity is a common toxicity that can result in severe hepatic damage, which can progress to liver failure. Traditional liver markers, have limitations in early detection. **Aim:** The present work aims to evaluate the efficacy of miRNA-122 serum level in detecting the degree of liver affection in the early phases of acute paracetamol toxicity. **Methods:** This prospective study was conducted by collecting demographic, clinical data and blood samples from 35 acute single paracetamol toxicity patients admitted to the Poison Control Centre of Ain Shams University. Liver function tests, serum miRNA-122 expression and paracetamol level were measured on admission, at 24 and 48 hours. 35 controls matched to age and gender, were used as a reference to the lab results. **Results:** The studied patients with acute paracetamol toxicity were 10 males (28.6%) and 25 females (71.4%). Mean age was 25.3 years ± 6.7. The levels of miRNA-122 on admission were statistically significantly higher in patients than in controls. The levels of ALT and INR increased statistically significantly over time, whereas paracetamol and miRNA-122 decreased statistically significantly over time. MiRNA-122 expression showed a strong positive correlation with the amount of paracetamol consumed, ALT levels ($p < 0.000$), and length of hospital stay, and a moderate correlation with INR ($p = 0.010$). **Conclusions:** This study provides evidence supporting the potential role of miRNA-122 as a biomarker for early detection of the degree of liver injury in acute paracetamol toxicity patients. MiRNA-122 demonstrated superior sensitivity and specificity compared to traditional liver markers.

Received in original form: 10 June 2023 Accepted in a final form: 8 July 2023

Key words MiRNA-122, Acute paracetamol toxicity, Acute liver injury ALI, Alanine aminotransferase (ALT), International normalized ratio (INR)

Introduction

Paracetamol is one of the most used analgesic and antipyretic drugs worldwide. Despite being safe at therapeutic levels, overdoses can cause acute liver injury (ALI), which in some cases can progress to acute liver failure (ALF) (Ramachandran and Jaeschkea, 2019). Paracetamol toxicity is one of the common toxicities seen in emergency rooms (Hendricson, 2011; Kominek et al., 2015). In Ain Shams University poison control center, 650-750 cases are seen annually which accounts for 4-5% of cases admitted to the center (PCC annual report 2020-2021).

Paracetamol toxicity causes liver injury that could be missed in the early routine laboratory investigations. This is due to the pattern of elevated levels of liver enzymes; alanine aminotransferase (ALT) and aspartate aminotransferase (AST). It is difficult to determine the extent of liver damage in the first 24 hours following paracetamol overdose because these enzymes increase within 24 hours and peak at 72 hours (Yoon et al., 2016).

Acetylcysteine is an efficient antidote for treating cases of paracetamol toxicity, but adverse reactions are seen in nearly 45 % of treated patients. In addition, treatment with acetylcysteine takes at least 20 hours to complete, resulting in significant hospital bed occupancy (Kerr et al., 2005).

The decision to start treatment depends on the dosage of consumed paracetamol and repeated checks for its blood concentration. And with minor elevation in the liver enzymes in the early hours of toxicity, there is always a state of clinical uncertainty regarding the unknown degree of liver cell injury which might lead to overtreating patients with a time-consuming and potentially harmful antidote or undertreating them, thus increasing the risk of ALI (Antoine et al., 2013).

Accordingly, new biomarkers are needed that identify or exclude liver toxicity early in the disease process so that appropriate medical care could be applied. This in term will lead to a decrease in morbidity and mortality (Larson et al., 2005; Vliegenthart et al., 2015).

Short non-coding nucleotides known as micro-RNAs (miRNAs) control the expression of genes and specific cellular proteins by targeting specific messenger RNAs (Elfimova et al., 2012). Micro-RNAs demonstrate regulatory functions related to cell growth, differentiation and development. They are associated with a large variety of diseases and are important to cellular physiological functions as well as to pathogenesis (Rana, 2007; Xu et al., 2016). Micro-RNAs are widely expressed in various body tissues, but some are specifically expressed in certain body tissues making them highly organ-specific (Girard et al., 2008).

Several miRNAs are expressed by the liver cells, where miRNA-122 is considered the most abundant hepatic miRNA accounting for more than 70% of the total miRNAs in adult human liver. MiRNA-122 interacts with many targets involved in the stress-response pathways as well as in the metabolic pathways (Coulouarn et al., 2009, Dear et al., 2018).

Accordingly, the current study aimed to evaluate the value of miRNA-122 serum level in detecting the degree of liver affection in early phases of acute paracetamol toxicity; and to compare it to the conventional laboratory detection methods.

Patients and Methods

Study design: The current study was conducted in two phases. The first phase was a case-control study to compare the miRNA-122 level in patients with acute paracetamol toxicity versus healthy controls. The second phase was a prospective cohort study to assess the role of miRNA-122 in the early detection of the degree of liver affection in patients with acute paracetamol toxicity.

Ethical considerations: Approval was granted by the Faculty of Medicine Ain-Shams University Research Ethics Committee (Approval number: R139/2023). Each patient, as well as each control participant, gave their informed consent. The collected specimens were coded and anonymously stored to ensure confidentiality.

Sample size: A sample size of at least 35 patients with paracetamol poisoning was needed, by using Power Analysis and Sample Size Software (PASS 15) (Version 15.0.10) for sample size calculation, at a confidence level of 95%, margin of error ± 0.15, and after assuming that the correlation between the level of miRNA-122 in patients with acute paracetamol toxicity and the degree of liver affection assessed by the level of liver enzymes is 0.80. A sample of 35 healthy controls was also included to compare the miRNA-122 level between patients with acute paracetamol toxicity and healthy controls.

Patients and controls: The study involved 35 patients who had been admitted to the Poison Control Centre of Ain Shams University Hospitals (PCC-ASUH) between January 2022 and June 2022 with a single acute paracetamol overdose. They were compared with a control group of 35 healthy people who were age- and gender-matched.

Inclusion and exclusion criteria of the patient group

- Inclusion Criteria: Patients aged 18 years or older, with a confirmed diagnosis of acute paracetamol toxicity based on history and laboratory investigations arriving within 8 hours post-ingestion.
- Exclusion Criteria: Patients with a history of chronic hepatic disease, pregnancy or known use of substances that affect liver functions (e.g: alcohol or anticoagulants), co-ingestion of other hepatotoxic agents, and pre-treatment before admission to the PCC.

Data collection tools: Data were gathered by using Patient information sheets and performing laboratory investigations.

Patient information sheets were divided into three sections:

- Demographic data (age, gender)
- Intoxication data (dose, route, form, manner of overdose, co-ingestions, pretreatment, and time from ingestion until the first blood sample)
- Clinical data (symptoms of toxicity such as vomiting and abdominal pain, vital signs, and signs of jaundice, hepatomegaly, and ascites).

Laboratory investigations: A plastic disposable syringe was used to draw venous blood samples from each patient and each control subject under aseptic procedures. Each patient underwent these tests three times: once at admission, again after 24 hours, and once again after 48 hours.

- The SPEKOL 11 analyzer was used to test the paracetamol blood level at a wavelength of 450 nm.
- *Total RNA extraction:* For the real-time PCR, mirVana PARIS kit was used to extract RNAs from plasma according to the manufacturer's protocol. This step was followed by organic extraction using both acid–phenol and chloroform. RNA purity was quantified by the NanoDrop ND-1000. Reverse transcription and TaqMan real-time PCR assays were done for microRNA.

Data management and Statistical analysis:

Data was tabulated and statistically analyzed using SPSS, version 20 (SPSS Inc., Chicago, IL). Repeated measures ANOVA test was used to compare laboratory markers levels overtime (followed by post-hoc Bonferroni test). Pearson correlation coefficient was used to correlate between quantitative variables. P-value ≤ 0.05 was considered statistically significant. ROC Curve analysis was done to detect the cut-off point for miRNA-122.

Results

Thirty-five patients with acute paracetamol toxicity (10 males (28.6%), 25 females (71.4%), mean age: 25.3 years ± 6.7) were included in this prospective analysis and compared with 35 healthy controls (9 males (25.7%), 26 females (74.3%), mean age: 27.6 years ± 7.1).

All patients were suicidal and intoxicated by the consumption of paracetamol tablets (only two cases had tramadol co-ingestion) with no pretreatment. There is no previous history of alcohol or therapeutic drugs use. Most of patients experienced vomiting without abdominal pain and jaundice. The mean delay time for receiving treatment was 6.8 hours ± 1.4. The mean duration of hospital stay was 4.4 days ± 2.2.

When compared to healthy controls, the levels of miRNA-122 were statistically significantly higher in

patients than in controls at the time of admission, as shown in Table 1.

In patients with acute paracetamol intoxication, the levels of ALT, INR, and PTT increased statistically significantly over time, whereas paracetamol and miRNA-122 decreased statistically significantly over time, as indicated in Table 2.

Over the follow-up period from admission till 48 hours after admission, the miRNA-122 expression showed significant positive correlation with the amount of paracetamol consumed, the delay time, ALT ($p < 0.000$) and the length of hospital stays, while it showed moderate positive correlation with INR ($p = 0.010$), as shown in Tables 3, 4, and 5.

Regarding the sensitivity and specificity, on arrival miRNA-122's area under the curve (AUC) for detecting liver damage brought on by acute paracetamol toxicity was (1.000), and at the cut-off point of (2.11), it demonstrated 100% sensitivity and 100% specificity.

Table 1. Baseline laboratory markers of patients with acute paracetamol toxicity in comparison to healthy controls

	Patient group on admission	Healthy controls	P
	Mean ± SD	*Mean ± SD*	
ALT (U/L)	34.1 ± 12.3	34.1 ± 5.7	0.990
INR (sec)	1 ± 0.1	1 ± 0.1	0.682
miRNA-122 (folds)	12.8 ± 6.9	0.2 ± 0.1	0.000*

Independent t test was used, P-value ≤ 0.05 is considered statistically significant, *highly significant

Table 2. Laboratory markers in patients' overtime (on admission, at 24 hours, and at 48 hours)

	On admission [a]	At 24 hours [b]	At 48 hours [c]	P-value			
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	Over-all	Bet. a & b	Bet. a & c	Bet. b & c
Paracetamol (ug/ml)	102.7 ± 37.2	7.4 ± 8.2	1.5 ± 0.8	0.000*	0.000*	0.000*	0.000*
ALT (U/L)	34.1 ± 12.3	1172.9 ± 1818.3	1577.9 ± 2308.5	0.000*	0.001*	0.000*	0.000*
INR (sec)	1 ± 0.1	1.3 ± 0.4	1.5 ± 0.5	0.000*	0.000*	0.000*	0.000*
miRNA-122 (folds)	12.8 ± 6.9	8.3 ± 5	2.8 ± 1.3	0.000*	0.000*	0.000*	0.000*

Repeated measure ANOVA test was used, P-value ≤ 0.05 is considered statistically significant, * highly significant

Table 3. Correlation between relative miRNA-122 expression and duration of hospital stay with other laboratory markers on admission

On admission		Dose (G)	Paracetamol (ug/ml)	ALT (U/L)	INR (sec)	miRNA-122	Duration of stay (days)
Dose (G)	**r**	1					
	P						
Paracetamol (ug/ml)	**r**	0.636**	1				
	P	0.000					
ALT (U/L)	**r**	0.220	-0.067	1			
	P	0.204	0.701				
INR (sec)	**r**	0.180	0.026	0.205	1		
	P	0.301	0.883	0.237			
miRNA-122 (folds)	**r**	0.689**	0.150	0.547**	0.430**	1	
	P	0.000	0.391	0.001	0.010		
Duration of stay (days)	**r**	0.651**	0.198	0.431**	0.434**	0.940**	1
	P	0.000	0.254	0.010	0.009	0.000	

Pearson correlation coefficient was used, P-value ≤ 0.05 is considered statistically significant. ** Strong positive correlation

Table 4. Correlation between relative miRNA-122 expression and duration of hospital stay with other laboratory markers at 24 hours

At 24 hours		Dose (G)	Paracetamol (ug/ml)	ALT (U/L)	INR (sec)	miRNA-122	Duration of stay (days)
Dose (G)	r	1					
	P						
Paracetamol (ug/ml)	r	0.610**	1				
	P	0.000					
ALT (U/L)	r	0.784**	0.389*	1			
	P	0.000	0.021				
INR (sec)	r	0.737**	0.387*	0.869**	1		
	P	0.000	0.022	0.000			
miRNA-122 (folds)	r	0.656**	0.411*	0.725**	0.704**	1	
	P	0.000	0.014	0.000	0.000		
Duration of stay (days)	r	0.651**	0.424*	0.642**	0.625**	0.961**	1
	P	0.000	0.011	0.000	0.000	0.000	

Pearson correlation coefficient was used, P-value < 0.05 is considered statistically significant. ** Strong positive correlation

Table 5. Correlation between relative miRNA-122 expression and duration of hospital stay with other laboratory markers at 48 hours

At 48 hours		Dose (G)	Paracetamol (ug/ml)	ALT (U/L)	INR (sec)	miRNA-122	Duration of stay (days)
Dose (G)	r	1					
	P						
Paracetamol (ug/ml)	r	0.449**	1				
	P	0.007					
ALT (U/L)	r	0.804**	0.244	1			
	P	0.000	0.158				
INR (sec)	r	0.767**	0.236	0.922**	1		
	P	0.000	0.172	0.000			
miRNA-122 (folds)	r	0.588**	0.318	0.530**	0.548**	1	
	P	0.000	0.063	0.001	0.001		
Duration of stay (days)	r	0.651**	0.162	0.691**	0.695**	0.861**	1
	P	0.000	0.353	0.000	0.000	0.000	

Pearson correlation coefficient was used, P-value < 0.05 is considered statistically significant. ** Strong positive correlation

Discussion

Early detection of the degree of liver affection in cases of paracetamol toxicity is crucial for optimal patient management and improved outcomes (Bernal et al., 2010). The use of more sensitive and specific biomarkers for early detection of liver injury could help optimize patient management, ultimately reducing morbidity and mortality associated with acute paracetamol toxicity.

The current study included thirty-five patients admitted to the Poison Control Center Ain Shams University with acute paracetamol toxicity. In the early hours post ingestion in cases of acute paracetamol toxicity, the diagnosis of acute liver injury and the initiation of antidote treatment depends mainly on paracetamol serum level plotted on Rumak Mathew nomogram as the rise in liver transaminases is not seen except several hours post ingestion (Shankar & Mehendale, 2006; Olson, 2012)

The role of microRNA-122 (miRNA-122) in the early detection of liver injury in patients with acute paracetamol toxicity is an area of increasing interest, as this small non-coding RNA molecule has been found to be involved in the regulation of liver homeostasis and is highly abundant in the liver (Bandiera et al., 2015). Elevated levels of miRNA-122 in the bloodstream can be indicative of liver damage and may serve as a potential biomarker for the early detection of liver injury (Wang et al., 2009; Carreiro et al., 2020).

In cases of liver damage, the specificity of alanine aminotransferase (ALT) and international normalized ratio (INR) over aspartate aminotransferase (AST) and partial thromboplastin time (PTT) is noteworthy. ALT is considered a more specific marker of liver injury compared to AST, as it is predominantly found in liver cells, whereas AST is also present in other tissues, such as skeletal muscle, heart, and kidneys (Giannini et al., 2005). INR, is a measure of

the liver's synthetic function, specifically related to the production of clotting factors, as most of these factors are produced in the liver (Tripodi and Mannucci, 2011). In the context of liver injury, INR is a more reliable indicator of liver function impairment compared to PTT. While PTT measures the intrinsic and common coagulation pathways, it can be influenced by multiple factors unrelated to liver function, such as deficiencies in specific clotting factors or the presence of antiphospholipid antibodies (Francis and Hursting, 2005).

Accordingly, the current study considered the measurements of ALT and INR as indicators for liver affection and investigated the differences in their expression and the expression of miRNA-122 in cases of acute paracetamol toxicity.

In the current study, the levels of miRNA-122 were found to be significantly higher in patients with acute paracetamol toxicity when compared to healthy controls at the time of admission (P-value<0.000). However, there was no significant difference between the levels of ALT and INR between patients and controls (P-value 0.990 and 0.682 respectively). This result is consistent with the findings of a previous study performed by Dear et al. (2018), who reported an increase in miRNA-122 levels in patients with paracetamol-induced liver injury. Moreover, Antoine et al. (2013) reported that new biomarkers other than liver enzymes that aid in early detection of ALI are needed.

During the course of hospital stay, there was a highly significant increase in the levels of ALT and INR seen in the samples taken at 24 and 48 hours when compared to controls and also when compared to one another denoting very high differences of the measured values over time. Contrarily, the levels of miRNA-122 showed a highly significant decrease over time in samples taken at 24 and 48 hours when compared to controls and also when compared to one another. Similar findings were reported by Antoine et al. (2013) and Dear et al. (2018) who concluded that miRNA-122 levels have been suggested as a more sensitive and specific biomarker than traditional liver injury markers, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Correlating the level of miRNA-122 in the three samples on admission, at 24 and 48 hours to other findings in the current study that confirms the occurrence of ALI, a strong positive correlation was observed between miRNA-122 expression and established markers of liver damage, such as ALT, and the amount of paracetamol consumed and the length of hospital stay. These findings suggest that miRNA-122 can be utilized as a biomarker for the severity of liver injury in patients with acute paracetamol toxicity. This is in line with the findings of a study by Liu et al. (2018), which demonstrated that miRNA-122 could predict the degree of liver injury in patients with paracetamol overdose.

Moreover, the moderate correlation between miRNA-122 and the international normalized ratio (INR) found in the current study indicates that miRNA-122 could also be potentially useful for monitoring coagulation abnormalities associated with liver injury, as INR is an important marker of liver synthetic function (Tripodi and Mannucci, 2011).

The utility of the findings of the current study are numerous. MiRNA-122 levels as an early biomarker for liver injury in paracetamol toxicity offers several advantages over traditional liver markers, such as ALT and INR. MiRNA-122 levels increase earlier in the course of liver injury compared to ALT and INR, enabling prompt detection of toxicity before significant liver damage occurs. Additionally, miRNA-122 has been suggested to be a more specific marker for liver injury, as it is predominantly expressed in the liver, whereas ALT and INR can be influenced by factors unrelated to liver injury, such as muscle damage and coagulation disorders, respectively (Tripodi and Mannucci, 2011; Bandiera et al., 2015). Therefore, the incorporation of miRNA-122 as a biomarker in the early detection of paracetamol toxicity has the potential to improve the accuracy and timeliness of diagnosis, allowing for more effective patient management and potentially reducing the morbidity and mortality associated with acute liver injury.

In the current study, the ROC curve analysis revealed that on arrival miRNA-122 has an area under the curve (AUC) of 1.000, signifying its outstanding ability to discriminate between patients with liver damage and those without at a cut-off point of (2.11) miRNA-122 demonstrated 100% sensitivity and 100% specificity. This indicates that miRNA is able to correctly identify all patients with liver injury and exclude those without, making it a highly reliable diagnostic tool. This finding will be very helpful in stratifying patients with acute paracetamol toxicity and normal liver parameters on arrival where miRNA level would be able to point out severity of cases and anticipated liver damage. This could ultimately aid in improving patient outcomes by helping clinical decision makers in the early detection of liver injury and enabling timely intervention to prevent further damage.

The limitation of this study is the relatively small sample size. Further research with larger cohorts and a more diverse population is needed to validate the utility of miRNA-122 as a biomarker for early detection of liver injury and predicting the severity of cases and anticipated liver damage in patients with paracetamol toxicity.

Conclusion

In conclusion, the current study adds to the growing body of evidence supporting the role of miRNA-122 as a potential biomarker for the early detection of liver injury in patients with acute paracetamol toxicity. The findings from the current study suggest that miRNA-122 levels can be useful in the early detection and identification of the severity of liver injury in patients with acute paracetamol toxicity, even in cases where traditional liver parameters (e.g., ALT and INR) may still be within normal ranges. In addition, the cut-off value of miRNA could serve as a valuable tool for clinicians to assess the severity of liver injury and plan appropriate patient management strategies.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not- for-profit sectors; it was totally funded by the authors. The authors declare that there is no conflict of interest.

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دور miRNA-122 كمتنبئ مبكر لدرجة تأثر الكبد لدى المرضى الذين يعانون من التسمم الحاد للباراسيتامول والذين تم حجزهم بمركز علاج التسمم بمستشفيات جامعة عين شمس

سهى عشرى[١], سلمى إبراهيم عبد القادر[١] و مها مجدى وهدان[٢]و رانيا حسين[١]

الملخص العربي

الخلفية العلمية: تعتبر سمية الباراسيتامول هي واحدة من أكثر السميات شيوعًا والتي تؤدي إلى إصابة كبدية خطيرة يمكن أن تؤدى إلى فشل كبدي شديد. وتعتبر التحاليل التقليدية للكبد، لها محدودية خاصة في الاكتشاف المبكر. **الهدف من البحث**: يهدف العمل الحالي إلى تقييم فعالية MiRNA-122 في الكشف عن درجة إصابة الكبد في المراحل المبكرة لتسمم الباراسيتامول الحاد. **طريقة البحث**: أجريت هذه الدراسة الاستطلاعية من خلال جمع البيانات الديموغرافية والسريرية وعينات الدم من ٣٥ مريضاً مصاباً بالتسمم الحاد للباراسيتامول والذين تم حجزهم بمركز علاج التسمم بجامعة عين شمس. تم قياس تحاليل وظائف الكبد، وتحليل miRNA-122 بمصل الدم ومستوى الباراسيتامول عند الحجز، وبعد٢٤ و ٤٨ ساعة. إلى جانب ٣٥ مريض للعينة الضابطة مطابقة للعمر والجنس، كمرجع للنتائج المعملية. **نتائج البحث:** كان مرضى التسمم الحاد للباراسيتامول الخاضعين للدراسة ١٠ ذكور (٢٨.٦٪)، و٢٥ إناث (٧١.٤٪) متوسط أعمارهم ٢٥.٣ سنة ± ٦.٧. كانت مستويات miRNA-122 عند الحجز أعلى بشكل إحصائي في المرضى عن المجموعة الظابطة كما زادت مستويات الالنين ترانساميناز والنسبه الطبيعيه الدوليه لتجلط الدم بشكل ملحوظ إحصائيًا بمرور الوقت، في حين انخفض الباراسيتامول وmiRNA-122 بشكل كبير إحصائيًا بمرور الوقت كما أظهر تغيير MiRNA-122 ارتباطًا إيجابيًا قويًا بكمية الباراسيتامول المستهلكة، ومستويات الالنين ترانساميناز (p<0.000)، وطول الإقامة في المستشفى، وارتباط متوسط مع النسبه الطبيعيه الدوليه لتجلط الدم (P = 0.010). **الاستنتاجات**: تقدم هذه الدراسة أدلة تدعم الدور المحتمل لـ miRNA-122 كمؤشر حيوي للكشف المبكر عن درجة إصابة الكبد في المرضى الذين يعانون من التسمم الحاد للباراسيتامول. أظهر MiRNA-122 حساسية وخصوصية فائقة مقارنة بالتحاليل الكبد التقليدية.

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