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ORIGINAL ARTICLE

# Acetaminophen overdose treatment in patients admitted to two tertiary centers in Oman, variation and pitfalls

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## ABSTRACT

**Objectives:** This study aimed to assess treatment pitfalls and deviations from guidelines in two tertiary centers, focusing on the utilization of activated charcoal (AC), the timing of acetaminophen (APAP) level assessments, proper plotting of levels on the Rumack-Matthew Nomogram, and the administration of N-acetylcysteine (NAC). In addition, to explore the cost-effectiveness of variations in management.

**Methods:** A multi-center, descriptive retrospective study was conducted from March 2016 to December 2017 at Sultan Qaboos University Hospital and from January 2016 to December 2017 at Royal Hospital.

**Result:** Out of 110, 66 patients were presented within 4 hours post-ingestion while 29 were between 4-8 hours post-ingestion, of which 8 (12.1%) and 5 (17.2%) patients, respectively, were administered AC. Furthermore, 47.3% of APAP levels were not plotted on the nomogram. In the subset of patients presenting within 4 hours post-ingestion, 35 patients (53%) had their first APAP level sent before 4 hours. Out of the 110 patients, 22 (20.0%) required NAC based on the physician's assessment, with only 14 of them being at or above the treatment line. Surprisingly, two of these patients did not receive NAC. Overall, 91.8% experienced full recovery. In addition, unnecessary repetitions of 41.8% for APAP levels and 35.5% for liver function tests occurred within the first 24 hours of presentation. Furthermore, 30.6% of patients were admitted despite having levels below the therapeutic line and no history of co-ingestion.

**Conclusion:** Guidelines and pitfalls deviation in the management of APAP overdose are prevalent in emergency practices in two tertiary hospitals in Oman.

**Keywords:** Acetaminophen, overdose treatment, Oman, variation, pitfalls.

## Introduction

Paracetamol Acetaminophen (APAP) overdose can result in hepatotoxicity, representing the most frequently reported poisoning in the United States and exhibiting the highest mortality rate, with over 100,000 exposures and 300 reported deaths annually [1]. The approved antidote for Paracetamol overdose is N-acetylcysteine (NAC), available in both oral and intravenous (IV) formulations [1]. The treatment protocol for Paracetamol toxicity involves the administration of intravenous N-acetylcysteine (IV-NAC), a three-step process that, unfortunately, is prone to medication errors, with occurrences reported at a notable frequency [2].

The assessment of the risk of hepatotoxicity in the absence of NAC is established through the application of the Rumack-Matthew nomogram. When the APAP level surpasses or equals the designated treatment line on the nomogram, it serves as a clear indication to initiate the administration of the antidote, NAC [3].

The occurrence of APAP overdose has been previously documented in Oman. Two studies, conducted in 2002 and 2003, highlighted APAP overdose as the predominant method of self-poisoning. The latter study specifically identified self-harm involving APAP overdose, constituting 18.2% of the overall methods of

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self-harm [4,5]. Despite these findings, prior research has not explored the timing of presentation and the standard of care. Notably, there has been no assessment of staff adherence to the NAC administration protocol.

Hence, this study aimed to assess the treatment variation in APAP overdose cases in Oman, investigating potential pitfalls in the management of APAP toxicity, and evaluating the associated outcomes.

## Subjects and Methods

This retrospective descriptive study took place at the emergency departments (EDs) of two tertiary care centers in Oman including Sultan Qaboos University Hospital (SQUH) and the Royal Hospital (RH), spanning 2 years. Data collection at the RH occurred from January 2016 to December 2017, while data from SQUH Hospital was collected between March 2016 and December 2017.

This study encompassed all patients who sought medical attention within 24 hours of acute APAP ingestion. Exclusions were made for individuals who presented with APAP ingestion after the 24-hour threshold, those whose toxicology reports were requested for reasons other than APAP overdose, and those undergoing investigations for alternative diagnoses such as hepatitis. In addition, patients who lacked adequate data and those who departed from the ED without receiving medical attention were also excluded.

All the essential patient characteristics, including age, gender, place of residency, previous suicidal attempts history, prior drug overdoses, comorbidities, and a history of psychiatric illness were gathered. The focus was on determining the prevalence of APAP toxicity among these individuals. Subsequently, the treatment variations were evaluated by documenting the timing of APAP level assessments concerning the time of ingestion, and whether these assessments correctly aligned with the APAP nomogram to ascertain the necessity for initiating NAC. The analysis also involved the identification of potential treatment pitfalls, such as delayed NAC administration, incorrect NAC dosages, and the timing of APAP level measurements—whether these were conducted too early or too late. Furthermore, the complications arising from APAP toxicity were examined, along with the assessment of the overall outcomes and cost-effectiveness associated with the variations in APAP toxicity management.

A comprehensive review of patients who presented to the ED with acute APAP ingestion between 2016 and 2017 was conducted. This involved utilizing the Al-Shifa electronic record system at RH and the Track Care electronic system at SQUH. The data collection process was performed directly through Microsoft Excel® software, and subsequent analysis was carried out using Statistical Package for the Social Sciences. The data were presented as frequency (N) and percentage (%) and associations were analyzed using the chi-square test where the value less than and equal to 0.05 was considered significant.

## Results

A total of 437 patients were enrolled in the study, with 51 from SQUH and 386 from RH. Among them, 110 patients met the inclusion criteria, while 327 were excluded (Figure 1).

The baseline characteristics of the patients revealed that 95.5% of individuals presenting with APAP toxicity had no comorbidities. Within the adult group, 88.9% of patients were female, while in the pediatric group, 65% were male (Table 1).

In the adult population, 39% concurrently used APAP with other drugs, and 72% exhibited symptoms, with vomiting being the most prevalent. Among children, 25% showed symptoms, with vomiting being the predominant symptom (Table 2).

Out of the 66 patients who arrived at the ED within 4 hours of ingestion, only eight received activated charcoal (AC). Furthermore, 7 of those patients who received AC were presented within 1-2 hours. Notably, 5 out of 29 patients who arrived after 4 hours (17.2%) received AC, even though it was not indicated (Figure 2).

Within the subset of patients who presented within 4 hours of ingestion, 35 out of 66 (53.0%) had their first APAP level sent early (before 4 hours). This represents a notable management pitfall, as sending the level before 4 hours does not alter the course of management and cannot be plotted on the nomogram (Figure 3).

Furthermore, only 52.7% were plotted on a nomogram. However, a total of 47.3% of APAP levels were not plotted on the nomogram in the ED. Consequently, these patients were either referred to the medicine department, where their levels were plotted or were discharged home

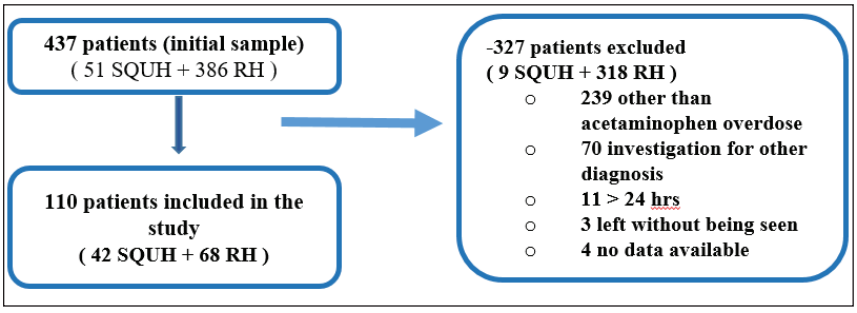


***Figure 1.*** *Patients included in the study.*

***Table 1.*** *Demographic features of the participants.*

| Variables | Frequency (%) | | | chi-square (*p*-value |
|---|---|---|---|---|
| | Male (*n* = 29) | Female (*n* = 81) | Total (*n* = 110) | |
| Center<br>SQUH<br>RH | <br>11 (37.9)<br>18 (62.1) | <br>31 (38.3)<br>50 (61.7) | <br>42 (38.2)<br>68 (61.8) | 0.001 (0.974) |
| Age group<br>Pediatric (=<12 years)<br>Adult (=>13 years) | <br>19 (65.5)<br>10 (34.5) | <br>9 (11.1)<br>72 (88.9) | <br>28 (25.5)<br>82 (74.5) | 33.31 (0.001) |
| Place of residency<br>Muscat<br>Outside muscat | <br>25 (86.2)<br>4 (13.8) | <br>76 (93.8)<br>5 (6.2) | <br>101 (91.8)<br>9 (8.2) | 1.65 (0.199 ) |
| Previous suicidal attempts among adult | 1 (3.4) | 9 (11.1) | 10 (9.09) | 33.34 (0.001) |
| Previous drug overdose | 1 (3.4) | 8 (9.9) | 9 (8.2) | 1.17 (0.278) |
| Past psychiatric history among adult | 1 (3.5) | 5 (6.2) | 6 (5.45) | 33.37 (0.001) |
| Comorbidities<br>None<br>Hepatitis B virus<br>Alcohol consumer<br>HTN | <br>28 (96.6)<br>0 (0)<br>1 (3.4)<br>0 (0) | <br>77 (95.1)<br>1 (1.2)<br>0 (0)<br>1 (1.2) | <br>105 (95.5)<br>1 (0.9)<br>1 (0.9)<br>1 (0.9) | 4.2 (0.517) |

***Table 2.*** *Clinical features of the participants.*

| | Dose of ingested APAP *N* (%) | | | | Combined with other drugs *N* (%) | Patients with symptoms *N* (%) | Chief symptom at ED presentation *N* (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <8g | 8-15g | >15g | unknown | | | Abdominal pain | Nausea | vomiting | AMS |
| Adults | 52 (63.4) | 20 (24.4) | 9 (11) | 1 (1.2) | 32 (39) | 59 (72) | 17 (28.8) | 14 (23.7) | 26 (44.1) | 2 (3.4) |
| Total | 82 (100) | | | | | | 59 (100) | | | |
| Pediatric | **<150 mg\kg** | **≥150 mg\kg** | | **unknown** | 2 (7.1) | 7 (25) | 2 (28.6) | 0 | 5 (71.4) | 0 |
| | 12 (42.9) | 10 (35.7) | | 6 (21.4) | | | | | | |
| Total | 28 (100) | | | | | | 7 (100) | | | |

AMS= Altered mental state.

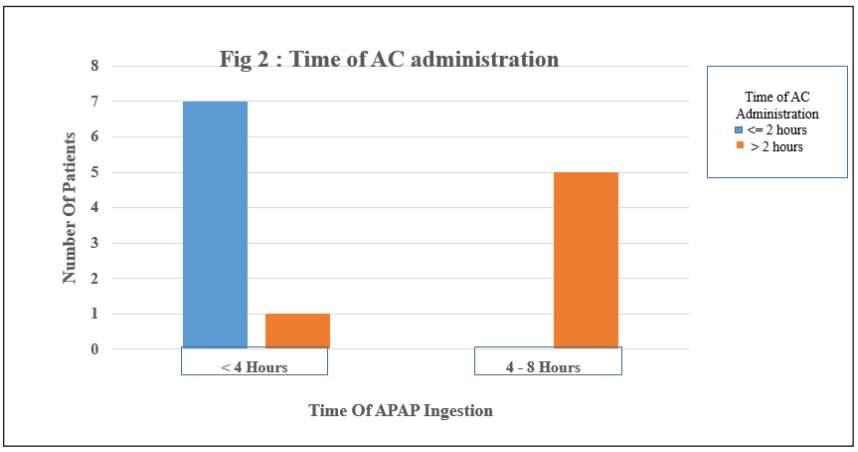


***Figure 2.*** *Time of AC administration.*

without having their levels plotted on the nomogram (refer to Figure 4).

The appropriateness of interpreting the APAP level using the nomogram for patients with measured APAP levels was assessed, excluding 10 patients whose levels were sent within 4 hours of ingestion and not repeated after 4 hours. Among the remaining patients, 86 (78.2%) had serum APAP levels below the treatment line. Surprisingly, 10 of them received NAC. Conversely, among those whose levels were at or above the treatment line, 12 out of 14 received NAC (Figure 5).

Among the eight patients who presented within 8 hours to the ED and had levels at or above the treatment line necessitating NAC, only three received NAC before 8 hours, while the remaining five received NAC after 8 hours, despite presenting early to the ED. In total, 12

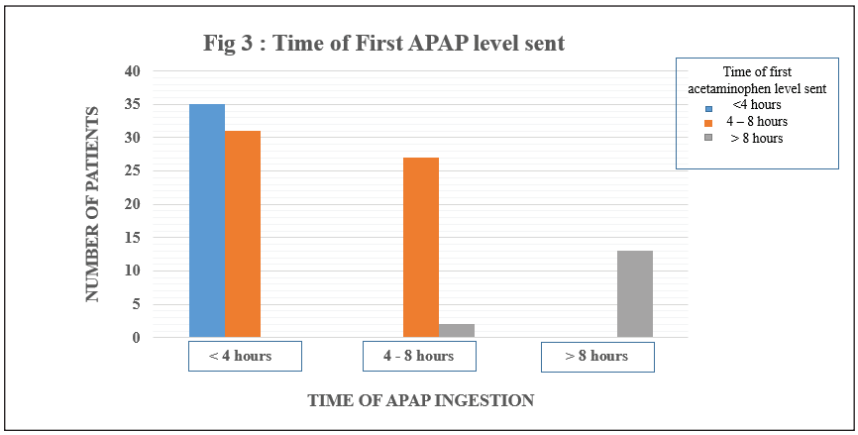


***Figure 3.*** *Time of first APAP level sent.*

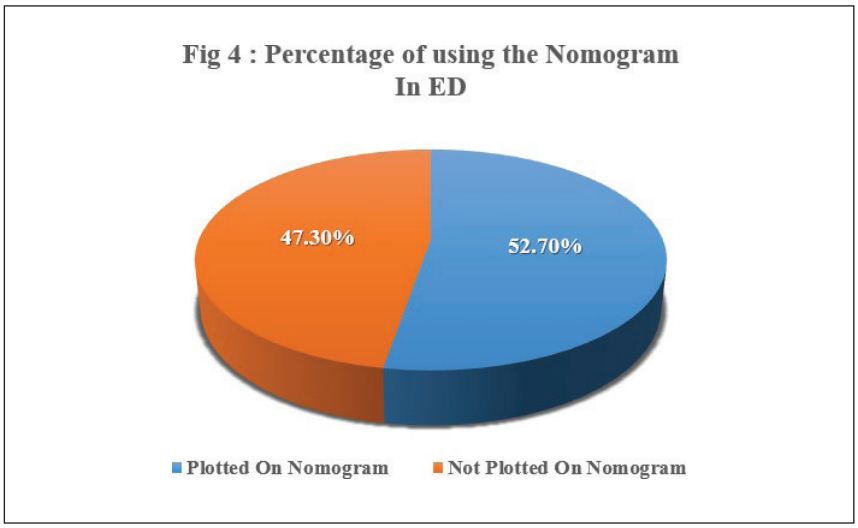


***Figure 4.*** *Percentage of using the nomogram.*

patients required NAC, with 10 receiving the correct NAC dosage for 21 hours, and two receiving NAC for 16 hours only (Table 3).

In patients who received NAC, 33.0% and 41.7% experienced no gap between the first and second infusions and between the second and third infusions, respectively. Notably, a 2-5 hours' delay between infusions was observed in 25.0% of patients (Table 4).

Forty-nine percent of the patients were discharged from the ED, while 41.8% were admitted to the adult medical ward, and 6.4% were left against medical advice. Remarkably, 91.8% of the patients achieved full recovery. Among the 110 patients, hepatic injury occurred in only one case due to delayed presentation to the Emergency Department (ED). The outcomes are unknown for 7.3% of the patients who left against medical advice. In terms of unnecessary practices, 41.8% of serum APAP levels and 35.5% of liver function tests (LFTs) were repetitively conducted within the first 24 hours of presentation. Furthermore, 30.6% of the patients were admitted despite having levels below the treatment line and no history of co-ingestion. Notably, 20.4% of these admitted patients were discharged in less than 24 hours (Table 5).

## Discussion

APAP is the most commonly encountered drug associated with toxicity resulting from overdose, and it has the potential to lead to severe complications, including fatal outcomes [6]. This retrospective study was designed to analyze the pitfalls in the management of APAP overdose.

As indicated by a prior study, the effectiveness of AC in managing APAP overdose has been demonstrated in reducing liver injury [7]. According to this study, all patients who presented within 1-2 hours of ingestion received AC, aligning with the recommended timeframe for its administration. Nevertheless, it is worth noting that AC was also administered to individuals who presented beyond 4 hours, a timeframe where its efficacy is less likely to be beneficial.

The application of the Rumack-Matthew nomogram is limited to patients with a known time of ingestion [8]. This study revealed that among those who presented with a known time of ingestion, 47.3% of APAP levels were not incorporated into the nomogram in the ED. Consequently, some patients were either referred to the medicine department or discharged without undergoing assessment using the nomogram. Notably, two patients

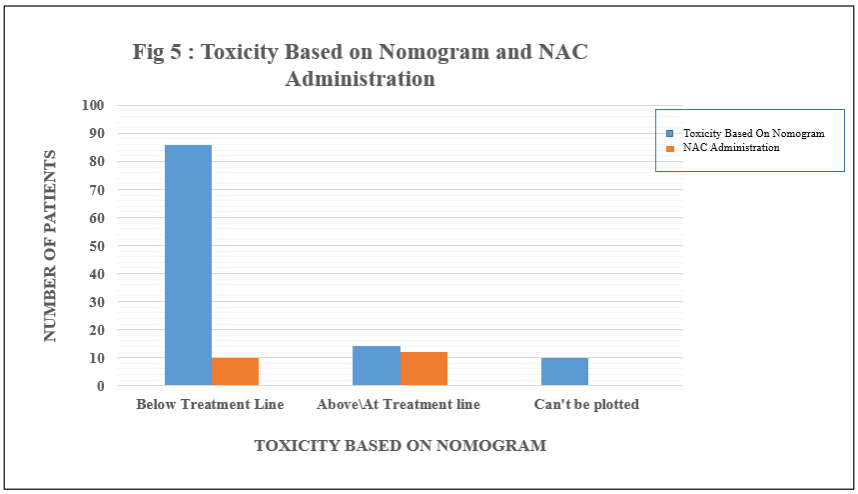


***Figure 5.*** *Toxicity based on nomogram and NAC administration.*

***Table 3.*** *Time of NAC administration and duration.*

| | | Time of ED presentation (Hour) *N* (%) | | | Time of NAC administration (Hour) *N* (%) | | Duration of the NAC (Hour) *N* (%) | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | <4 | 4–8 | >8 | <8 | >8 | 16 | 21 | |
| Toxicity based on nomogram | Above\At treatment line | 5 (41.7) | 3 (25) | 4 (33.3) | 3 (25) | 9 (75) | 2 (16.7) | 10 (83.3) | 12 (100) |

***Table 4.*** *Gap between NAC doses.*

| Toxicity based on nomogram | Above\At treatment line | GAP between firstst and second dose (Hours) *N* (%) | | | | GAP between second and third dose (Hours) *N* (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No GAP | ≤1 | 2-5 | >5 | No GAP | ≤1 | 2-5 | >5 | Total |
| | | 4 (33.3) | 4 (33.3) | 3 (25) | 1 (8.3) | 5 (41.7) | 4 (33.3) | 3 (25) | 0 (0) | 12 (100) |

***Table 5.*** *Secondary objectives.*

| Characteristics | Frequency (*N*) | Percentage (%) |
|---|---|---|
| Disposition | | |
| Discharge from ED | 54 | 49.1 |
| Admission to the medical ward | 46 | 41.8 |
| Admission to the pediatric ward | 1 | 0.9 |
| HD\ICU admission | 2 | 1.8 |
| LAMA | 7 | 6.4 |
| Outcome | | |
| Full recovery | 101 | 91.8 |
| Transaminases | 1 | 0.9 |
| Unknown | 8 | 7.3 |
| Repeated APAP level | | |
| First 24 hours | 46 | 41.8 |
| Level done > 2 times | 19 | 17.3 |
| Repeated LFT | | |
| First 24 hours | 38 | 34.5 |
| Test done > 2 times | 23 | 20.9 |
| Repeated coagulation | | |
| First 24 hours | 26 | 23.6 |
| Test done > 2 times | 15 | 13.6 |
| Unnecessary admission | | |
| The level below the treatment line | 15 | 30.6 |
| No combined drug | | |
| Hospital length of stay < 24 hours (Below treatment line, not combined with another drug) | 10 | 20.4 |

with levels above the treatment line were discharged from the ED without receiving NAC and were subsequently lost to follow-up.

One of the highlighted pitfalls in this study was the timing of sending the serum APAP level after ED presentation. To be plotted on the nomogram, the level should be sent after 4 hours from ingestion [9]. Surprisingly, among those patients who presented before 4 hours of ingestion, 53.0% had their first APAP level sent early (before 4 hours). It is crucial to emphasize that sending the level before 4 hours does not impact the management as it cannot be plotted on the nomogram, necessitating a repeat level after 4 hours.

Furthermore, among those who presented before 4 hours, there were two patients whose initial level was sent before 4 hours, and the repeat level exceeded the treatment line. Unfortunately, these patients received NAC after 8 hours of ingestion due to the delay in sending the second level.

Among those requiring NAC, the administration of NAC was unfortunately delayed beyond 8 hours, despite these patients presenting to the ED before the 8-hour window. Notably, two of them presented to the ED before 4 hours of ingestion. This delay represents a significant and serious pitfall in the management of paracetamol overdose, posing a heightened risk of hepatic injury [10].

Another identified pitfall in this study pertains to the dose of NAC. The established protocol in Oman for APAP toxicity involves a 21-hour IV protocol, with a loading dose of 150 mg/kg over 1 hour, followed by the second (maintenance) dose of 50 mg/kg over 4 hours and a third dose of 100 mg/kg over 16 hours [11-13]. Surprisingly, this study revealed that only 10 out of 12 patients received the correct dose of NAC for the full 21 hours, while two patients received NAC for only 16 hours.

For the management of APAP toxicity, patients must receive NAC without interruptions between the various infusions. A previous study noted that interruptions longer than 60 minutes occurred in some patients [5]. In the current study, approximately 66.7% and 58.3% of patients experienced a gap between the first and second doses, and between the second and third doses, respectively. Notably, a significant gap between doses of 2-5 hours was observed in 25.0% of patients.

Previous research has indicated that the late presentation of significant APAP overdose is a risk factor for hepatic encephalopathy and poor outcomes [14-16]. In the current study, only one patient who presented late developed hepatic injury. However, eight patients left against medical advice, with two of them having APAP levels above the treatment line. The clinical outcomes of these patients remain unknown. This emphasizes the importance of adequately educating patients about the risks associated with leaving the hospital against medical advice after a significant APAP overdose [17-19].

In terms of assessing the cost-effectiveness of the management, the study revealed that 41.8% and 35.5% of APAP levels and LFTs, respectively, were repetitively conducted unnecessarily within the first 24 hours. Furthermore, 30.6% of patients were admitted with a serum APAP level taken after 4 hours of ingestion, which was below the therapeutic line, and there was no other discernible reason for their admission. Studies have emphasized the guidelines and protocols regarding the repeated conduction of APAP levels along with LFTs [20,21].

The findings of this study highlighted the prevalence of management pitfalls in APAP overdose cases in the EDs in Oman. In response to these challenges, the National Management Guidelines for poisoning were introduced in December 2018. These guidelines encompass the management of common pharmaceutical agents, including paracetamol poisoning, to promote adherence to standardized protocols. In addition, the newly established Oman Poison Control Section of the Ministry of Health now provides clinical toxicology consultations from various hospitals in Oman. This initiative aims to enhance the correct management of APAP toxicity and mitigate the occurrence of pitfalls [22].

One of the limitations of this study was its retrospective design and relatively small sample size. In addition, the availability of data was limited, and there were occasional instances of missing information.

## Conclusion

Pitfalls in the management of APAP overdose and deviations from guidelines are prevalent in emergency practices in Oman. These shortcomings impact patients by causing delays in treatment administration and affect the healthcare system as unnecessary investigations contribute to cost implications. The establishment of the Oman Poison Control Section, along with the publication of the National Poisoning Guideline, is anticipated to enhance the overall management of poisonings in Oman. It is strongly recommended clinicians that proactively reach out to the Oman Poison Control Section for guidance and advocate for the accessibility of guidelines for consultation within their respective hospitals.

### List of Abbreviations

| | |
|---|---|
| APAP | Acetaminophen |
| AC | Activated charcoal |
| EDs | Emergency departments |
| LFTs | Liver function tests |
| NAC | N-Acetylcysteine |
| RH | Royal Hospital |
| SQUH | Sultan Qaboos University Hospital |


### Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

### Funding

None.


### Consent to participate

Informed consent was obtained from all the participants.

### Ethical approval

Approval for this research was obtained from the Medical Research Ethics Committees at both SQUH and RH.
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