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ORIGINAL ARTICLE

Sensitivity of dose-estimations for acute acetaminophen overdose in predicting hepatotoxicity risk using the Rumack-Matthew Nomogram

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Abstract

Timely assessment of acetaminophen concentration in overdose situations is not always available in resource-poor settings. The 150 mg/kg dose-estimate for acetaminophen is widely considered as criterion for acetaminophen overdose. Its sensitivity and specificity when compared to the 150 mg/L treatment line on the Rumack-Matthew Nomogram (150-treatment line) has rarely been evaluated. This is a retrospective chart review of acute acetaminophen overdose patients. We evaluated the sensitivity and specificity of the 150, 200 mg/kg and 8- and 10-g dose-estimates by plotting the serum acetaminophen levels and using 150-treatment line on the Nomogram as the treatment cut-off. A comparison of medical care costs was performed. We enrolled 784 cases for analysis. Median (IQR) age was 23 (20–28) years (81.9% female). There were 545 cases (69.5%) where the estimated ingested acetaminophen dose were ≥150 mg/kg and 406 cases (51.8%) with concentrations ≥150-treatment line. Hepatotoxicity and acute liver injury (ALI) occurred in 7.3% and 23.9%, respectively. The sensitivity and specificity of 150 mg/kg dose-estimate for the 150-treatment line were 92.6% (95% CI 89.6, 94.8) and 55.3% (95% CI 50.3, 60.2). Among patients with dose-estimate below150 mg/kg, none developed hepatotoxicity and 17 (7.1%) develop ALI. The administration of activated charcoal significantly decreased the risk of being above the 150-treatment line by half. In resource-poor setings, the use of 150 mg/kg dose-estimate as a stand-alone criteria for initiation of N-acetylcysteine therapy is satisfactory, especially when combined with decontamination with activated charcoal and follow up of aminotransferase at 24 h.

KEYWORDS
acetaminophen, hepatotoxicity, poisoning, risk assessment, Rumack-Matthew Nomogram

Abbreviations: 100-TL, the lines that parallels the 150 mg/L treatment line in Rumack Matthew Nomogram and intersects the concentration 100 mg/L at 4 h; 150-TL, 150 mg/L treatment line in Rumack Matthew Nomogram; 200-TL, the lines that parallels the 150 mg/L treatment line in Rumack Matthew Nomogram and intersects the concentration 200 mg/L at 4 h; C4, the extrapolated acetaminophen concentration at 4 h post ingestion.

1 | INTRODUCTION

Acetaminophen overdose is the most common cause of medication-induced hepatotoxicity. The timely administration of the antidote, N-acetylcysteine (NAC), within the 8-h golden period typically results in the best outcome. Conversely, a delayed onset of NAC therapy is associated with incidences of hepatotoxicity that can be as high as 45%.[1] Thus, the aim for most clinicians is to individualize and expedite the decision to start NAC therapy. A patient's individual risk for hepatotoxicity is assessed based on the timed serum acetaminophen concentration and interpreted in accordance with the Rumack-Matthew Nomogram.[2] The standard of care in most countries across the globe is to start NAC therapy if the serum acetaminophen level falls on or above the 150 mg/L-treatment line, defined as the line passing the 150 mg/L concentration at 4 h on the Nomogram.[2] For the past 35 years, healthcare facilities with the capability for rapid, clinically relevant acetaminophen concentration assays have used the150-treatment line as the pillar of safe and cost-effective treatment threshold.[1]

Alternatively, such laboratory capacity is not always present in many circumstances, and even within the same country there are great discrepancies in both the availability and the practical utility of acetaminophen levels. In Thailand, for example, only a handful of hospitals are capable of achieving the expected, clinically impactful 4-h turnaround time. Despite the fact that the majority of public urban tertiary hospitals all over the country are able to perform the test, the turnaround times can be greater than 12 h and up to 1 week. In addition, most community hospitals are unable to perform the test at all. The outsourcing of acetaminophen concentration assay has also been explored, with the conclusion that travel time and overall pricing usually preclude sending specimens to be analyzed.[3–6] In addition, even when most practitioners initially decide to start NAC based solely on the estimated ingested dose, the subsequent timely return of serum acetaminophen level will dictate whether such treatment will need to be continued. And in rural and district hospitals where obtaining acetaminophen level is not an option, physicians are forced to base the initiation, and indeed the continuation, of NAC therapy on the estimated ingested dose of 150 mg/kg alone.[2,5–7] Acetaminophen level remains an elusive clinical tool to most physicians in these healthcare facilities, and patients are obligated to being hospitalized and completing the full course of NAC.

On the other hand, there are various dose-estimate thresholds for toxicity from acetaminophen. For example, in many textbooks and guidelines in Western countries, the threshold of 200 mg/kg or 10 g in adults is in use, although questions regarding its accuracy in predicting toxicity often arise.[2,6] Several studies have compared the diagnostic validity of different dose-of-ingestion estimates (dose-estimates) with the available acetaminophen levels, using the 150 mg/L or the 200 mg/L treatment lines as the hepatotoxicity cutoffs. A retrospective study from Malaysia reports good sensitivity of 97.5% for dose-estimate thresholds of 8 g when using the 150 mg/L treatment line as reference. The values decrease to 89.3% and 60.2% when the 10 and 12 g dose estimates are used.[8] A study from Sri Lanka finds the dose-estimate of 150 mg/kg has 89% sensitivity against the 200-treatment line reference while having only a 5% specificity.[7] A retrospective study from the UK and Australia finds that the 10-g dose-estimate has an 85% sensitivity when using the 150 mg/L treatment line.[9] (Table 1) Although they differ in their study populations and methodologies, these studies reflect the reliance of practitioners of toxicology on the dose-estimate method in instituting early NAC therapy in real-world practices. Optimization of an appropriate dose-estimate threshold means initiating treatment in patients with reasonable risks for hepatotoxicity and minimizing the costs incurred by overtreatment with the antidote.[7–10] These diverse sets of data echo the reality that, despite its long-regarded use in toxicology, there is lacking evidence of sensitivity and specificity of the 150 mg/kg dose-estimate at predicting hepatotoxicity when using the 150 mg/L treatment line. And most importantly, there can be 2.5%–10.5% of patients who are undertreated and 39.4%–95% overtreated depending on which dose-estimate criteria are being applied.[2,11–13] Siriraj Hospital, a large tertiary-care hospital, is one of the very few hospitals in Thailand with rapid acetaminophen turnround times, a robust clinical toxicology service, and an established protocol for the management of acetaminophen intoxication. It represents an ideal environment where the accuracy of dose-estimates can be evaluated.

1.1 | Objectives

The primary objective is to evaluate the sensitivity and specificity of the dose-estimate threshold of 150 mg/kg (dose-per-kg estimate) in

TABLE 1 Sensitivities and specificities of acetaminophen dose for acetaminophen concentration treatment lines in previous publications

Dose threshold	Treatment line (mg/L)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	References
150 mg/kg	200	89	5	[7]
8 g	150	97.5 (92.9, 99.5)	60.6 (52.8, 68.0)	[8]
8 g	100	0.81 (0.78, 0.85)	0.50 (0.47–0.53)	[9]
10 g	150	89.3 (82.3, 94.2)	65.3 (57.6, 72.4)	[8]
10 g	150	0.85 (0.78, 0.89)	0.61 (0.57, 0.64)	[9]
12 g	150	61.2 (51.9–69.9)	86.5 (80.4, 91.2)	[8]
16 g	100	0.50 (0.45, 0.54)	0.88 (0.85, 0.90)	[9]

predicting hepatotoxicity risk when using the 150 mg/L-treatment line of the Rumack-Matthew Nomogram as the gold standard in adults with acute acetaminophen overdose. In addition, we aim to perform a comparison of costs between the dose-estimate method versus the conventional serum-level method. The clinical validities of the 200 mg/kg, 8 and 10 g are also appraised.

2 | MATERIALS AND METHODS

This is a retrospective review of medical records of patients who presented with acetaminophen overdose and had at least one serum acetaminophen concentration drawn at the time of presentation at Siriraj Hospital, a tertiary care university hospital in Bangkok, Thailand, between the period of January 1, 2007, to December 31, 2016. Patients are included in the study if the overdose is acute, defined as having ingested the overdose of acetaminophen within a 1-h period. Specifically, the overdose is preliminarily defined as ingestion above therapeutic doses of 4 g/day in adults or 75 mg/kg/day in children. Other inclusion criteria are being over 12 years of age, known time of ingestion, known body weight, and known dose of ingestion. Patients are excluded if the overdose is classified as staggered (ingestion period longer than 1 h), mixed, involves delayed-released preparation. Patients are also excluded if the first acetaminophen concentration is drawn before 4 h or after 24 post-ingestion or if the time of ingestion is unclear. Extracted data includes demographic data, weight, types and doses ingested, serum acetaminophen concentration, clinical chemistry results, treatment received, clinical outcomes, and length of stay. In patients with more than one available acetaminophen concentration, the earliest value is used for analysis. The protocol is approved by Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University.

In using the Rumack-Matthew Nomogram, the terms 200 mg/L (200-TL), 150mg/L (150-TL) and 100 mg/L (100-TL) are used to signify the pre-determined treatment lines that intersect the concentrations 200, 150 and 100 mg/L at 4 h. For sensitivity and specificity calculations, the 150-TL is used as the primary gold standard cutoff for NAC initiation. The UK's treatment line of 100 mg/L (100-TL) at 4 h is also used as a secondary gold standard.[14] The dose-estimates used, taken from conventional published literature, are 150 mg/kg, 200 mg/kg, 8 g, and 10 g.[6,8,9] The extrapolated acetaminophen concentration at 4 h post ingestion(C_4) is calculated using the formula $C_4 = C_t/2e^{-(0.693/4)t}$ where C_t is the acetaminophen concentrations and t is the time lapse in hours between ingestion and blood sampling. Clinical outcomes of hepatotoxicity is defined as serum aminotransferase of ≥1000 U/L and acute liver injury (ALI) as serum aminotransferase level of 50 U/L or a doubling of the enzymes from initial levels.[15] The time-to-presentation is classified as early if the initial blood sample for acetaminophen is drawn within 7 h post-ingestion and as late if done beyond 7 h. This time limit is selected because it is the uppermost limit of the 8-h golden period at which time patients can present and still have the full protection of NAC therapy.

The standard treatment protocol for acute acetaminophen poisoning at Siriraj Hospital during the study period consists of gastrointestinal decontamination and a 21-h, three-bag NAC regimen (300 mg/kg). Enteral NAC is used only if intravenous NAC was not tolerated or contraindicated. Activated charcoal was administered if the patient presented within 4 h post-ingestion.

The cost comparison for each patient in the study is made by calculating the cost of treatment and investigation, including antidote, hospital stay, and laboratory test, that would have occurred between the two scenarios encountered by the treating physician where serum acetaminophen is available versus not available. The costs of treatment and medical services are calculated based on prices listed by public hospitals under the Ministry of Public Health, Thailand, in the 2021 fiscal year.

2.1 | Statistical analyses

Descriptive statistics are reported by frequency with percentages and means with standard deviations for categorical and continuous variables, respectively. Median and interquartile range are used if continuous variables have non-normal distribution. Student's *t*-test or Mann–Whitney *U* test are used to test differences of continuous variables. Categorical data are analyzed with a Chi-squared test or Fish's exact test. Spearman's correlation test is used to test the correlation between ingested acetaminophen dose and the estimated acetaminophen concentration at 4 h (C_4). An alpha value of 0.05 is applied for statistical significance. Sensitivity, specificity, positive predictive value and negative predictive values with their 95% confidence intervals are estimated. Receiver operating characteristic curves (ROC curve) and the areas under the curve (AUC) are used to evaluate the diagnostic accuracies. Maximal Youden index is used to indicate the optimal cutoff values.[16]

3 | RESULTS

During the study period, there were 1286 patients who had the diagnosis of acetaminophen overdose and available acetaminophen concentrations. Five hundred and two cases were excluded due to unknown ingestion time (74), initial acetaminophen concentration sampled before 4 h or after 24 h post-ingestion (36), mixed overdose (119), staggered overdose (43), overdose involving modified-release preparations of acetaminophen (3), unknown body weight (108), unknown ingested dose (42), parenteral acetaminophen exposure (3) and age below 12 years (74). In total, 784 cases were included in the analysis (Figure 1). There were 642 females (81.9%) with a median age of 23 years (IQR 20–28, range 13–67). Median body weight was 51 (IQR 46–59) kg. Median ingested acetaminophen dose was 15 000 (range 5500–75 000) mg and median average dose by body weight was 250 (range 61.5–1296.3) mg/kg. Cases were classified into 480 early- and 304 late-presenters. Medians of the measured and extrapolated 4-h (C4) concentration were 128.6

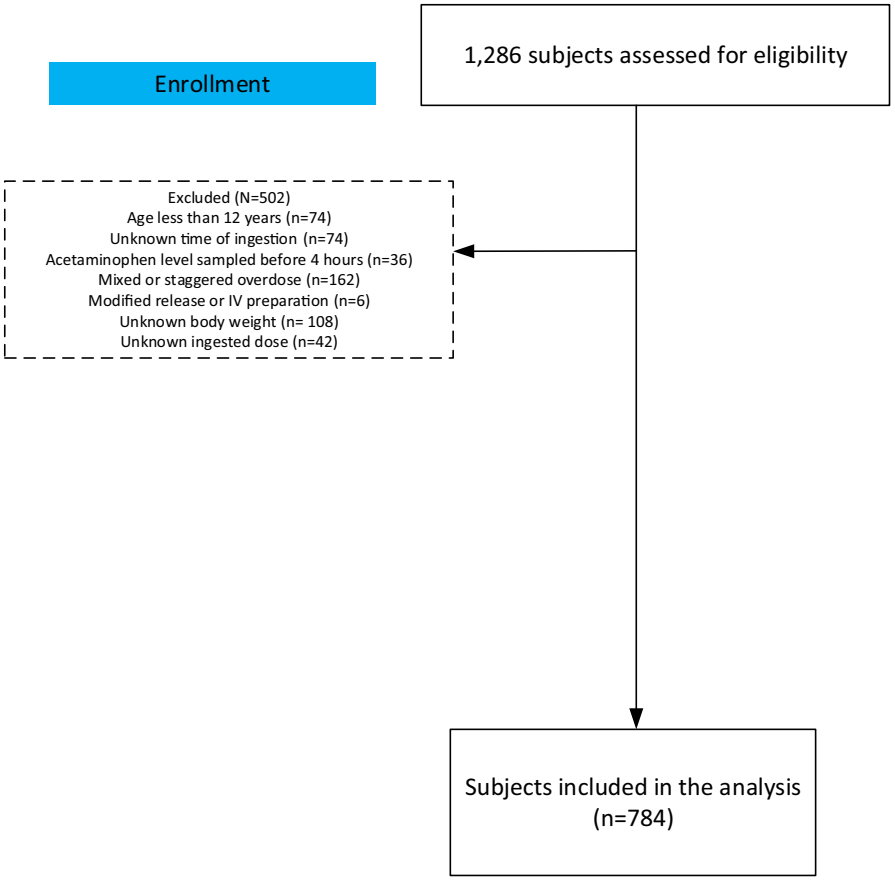

FIGURE 1 Patient enrollment flowchart

(IQR 79.9–178.3) and 179.3 (IQR 130.2–298.1) mg/L, respectively. Decontamination with activated charcoal was performed in 315 (40.2%) patients. Four hundred and six cases (51.8%) had serum acetaminophen concentration at or above 150-TL. Hepatotoxicity and acute liver injury occurred in 57 (7.3%) and 187 (23.9%), respectively. Patients whose acetaminophen concentrations were at or above the 150-TL had larger ingested dose, higher average dose per body weight, and were more likely to be late presenters and to experience hepatotoxicity and acute liver injury. The proportion of patients who received decontamination with activated charcoal was smaller in those with acetaminophen levels at or above the 150-TL. (Table 2) (Figure 2A,B).

The sensitivity and specificity of the 150 mg/kg dose-estimate at predicting serum level in the hepatotoxic range, when using the 150-TL, was 92.6% (95%CI 89.6–94.8) and 55.3% (95%CI 50.3–60.2), respectively. Concurrently, when using the 100-TL as reference, the sensitivity remained unchanged while the specificity increased to 89.7% (95%CI 84.9, 93.1). On the other hand, when using the 200 mg/kg dose-estimate as a cutoff, the specificity increased to 62.4 (95%CI 57.4–67.2) %, while sensitivity decreased to 79.3 (95%CI 75.1–83.0) % for 150-TL. Both sensitivities and specificities decreased when using the dose-estimate cutoffs of 8 and 10 g. (Table 3) When using the150-TL as reference, the ROC curves of ingested dose and average dose-estimate yielded areas under the curve (AUC) 0.722 (95%CI 0.689–0.753) and 0.748 (95% CI 0.717–0.779), respectively. Overall, the AUC of an average dose was significantly larger than that of an ingested dose ($p < .001$). The optimal cutoffs were 149.25 mg/kg and 11 g, respectively. ROC analyses of average dose in patients with and without activated charcoal decontamination yielded AUCs 0.816 (95% CI 0.765–0.860; optimal cutoff 169.49 mg/kg) and 0.701 (95% CI 0.659 to 0.741; optimal cutoff 140.65 mg/kg), respectively.

The average dose-estimate demonstrated significant correlation with the extrapolated acetaminophen concentration at 4 h (C_4), with a correlation coefficient of 0.267 ($p < .001$). The dose-estimate above 150 mg/kg was associated with acetaminophen concentrations above the 150-TL, hepatotoxicity and acute liver injury. (Table 4). Conversely, when the dose-estimate was below 150 mg/kg, no hepatotoxicity was found, but the cumulative incidence of acute liver injury was 7.1%. Three out of 81 cases (3.7%) whose dose-estimates were between 150 and 199 mg/kg developed hepatotoxicity, while 17 (21.0%) developed acute liver injury. Administration of activated charcoal was associated with a risk ratio of 0.46 (95%CI 0.38–0.55, $p < .01$) for being above the 150-TL when compared to those with no activated charcoal.

Among 239 patients with dose-estimates below 150 mg/kg, 17 (7.1%) developed ALI. There were no significant differences in the dose-estimates when compared with non-ALI cases. ALI cases had higher extrapolated acetaminophen concentrations at 4 h, were more likely to be late presenters, and be treated with NAC, but were less likely to receive activated charcoal when compared with non-ALI cases. (Table 5) There was no significant difference in the initial aminotransferases between ALI and non-ALI cases. Among ALI

TABLE 2 Characteristics of patient whose serum acetaminophen concentrations were above and below 150-treatment line

Characteristics	All ($n = 784$)	≥150-Treatment line ($n = 406$)	<150-Treatment line ($n = 378$)	*p*-value
Age (median (IQR), years)	23 (20–28)	23 (20–27)	23 (20–28)	.185
Female (count (%))	642 (81.9)	335 (82.5)	307 (81.2)	.638
Ingested dose (mg)	15 000 (10 000–20 000)	15 000 (10 000–20 000)	10 000 (9000–15 000)	<.01
Average ingested dose (mg/kg)	250.0 (185.2–384.6)	281.6 (200–400)	212.8 (138.9–332.0)	<.01
Late presentation	304 (38.8)	217 (54.3)	87 (23.0)	<.01
Blood sampling time post-ingestion (hours)	4 (6–9)	7 (5–10)	4.5 (4.0–7)	<.01
Acetaminophen concentrations (mg/L)	128.6 (79.9–178.3)	162.0 (114.5–205.9)	88.30 (64.7–113.7)	<.01
C4 (mg/L)	179.3 (130.2–298.1)	251.5 (191.5–379.6)	90.7 (60.8–125.1)	<.01
Activated charcoal	315 (40.2)	95 (23.4)	220 (58.2)	<.01
Vomiting	321 (40.9)	162 (39.9)	159 (42.1)	.538
Initial AST (U/L)	15 (13–22)	15 (12–22)	17 (13–22)	.522
Initial ALT	13 (9–19)	13 (9–20)	13 (10–19)	.499
NAC therapy	376 (66.9)	261 (100)	115 (30.4)	<.01
Hepatotoxicity	57 (7.3)	57 (14.0)	0	<.01
Acute liver injury	187 (23.9)	170 (41.9)	18 (4.8)	<.01

Abbreviations: ALT, aspartate aminotransferase; AST, aspartate aminotransferase; C4, acetaminophen concentration at 4 h as derived by back extrapolation; IQR, interquartile range.

cases, peak AST and ALT ranged from 45 to 358 and 65 to 394 U/L, respectively (upper normal limits: AST 32, ALT 34 U/L). In all cases, aminotransferase values were detected to be above 50 U/L at approximately 24 h post-ingestion.

When calculating the treatment cost, we assumed that those with dose-estimates of 150 mg/kg or more were treated with NAC and their expenses were calculated based on the current practice of using a 21-h, three-bag intravenous 300 mg/kg NAC regimen. The presumed body weight for this calculation was 51 kg, the median weight for subjects in our study. The approximate expense for NAC treatment, including hospitalization and laboratory investigation costs, was 2647 Baht/case (81.4 USD/case). When using dose-estimate, 545 cases would have been treated, totaling 1 422 615 baht (44 388.2 USD). In actuality, 406 patients had serum acetaminophen that was above the 150-TL. As such, the total expense for this group, including serum acetaminophen measurement, was 1 238 182 Baht (38 097.9 USD). Therefore, assuming all other conditions being equal, having access to timely acetaminophen concentration analysis can help shorten the hospitalization time and potentially save approximately 14.2% or 375.1 baht (11.5 USD) in treatment cost per case. However, keeping in mind that serum acetaminophen measurements themselves cost approximately 300 baht (9.2 USD) per test, the apparent benefit of cost-saving nearly disappeared.

4 | DISCUSSION

Despite the overwhelming number of publications from Western countries which recommend the use of acetaminophen concentrations as the gold standard for determining the risk of hepatotoxicity in an acute overdose, such a tool remains elusive for the majority of clinicians who practice toxicology in resource-limited settings such as Thailand and around the world.[9,17] And while it is true that dose-estimation is seen as a sub-optimal method for determining the initiation of NAC therapy, it continues to be a requisite in these parts of the world.[9,10] An informal survey among 83 physicians from 63 hospitals in Thailand who utilize the Siriraj Hospital Poison Information and Clinical Toxicology Service reveals that only 22 hospitals possess the capability to perform acetaminophen level assay and the turnaround times range from within 4 h (4 hospitals) to 24 h (10 hospitals) and beyond 24 h (8 hospitals). A guideline that specifies a sensitive and reasonably specific parameter for dose-estimate cutoff, together with watchful observation and monitoring, are required for safe, efficient, and timely management of patients. As such, striking a critical balance between a sufficiently low cutoff of dose-estimate to allow for NAC therapy of the at-risk patients while minimizing the need for unnecessary antidote administration and hospital stay is the key.

The cumulative incidence of hepatotoxicity (7.3%) in this study is comparable to the previously reported rates in Asian populations.[18–20] The dose-estimate threshold of 150 mg/kg demonstrates good sensitivities when using both the 150 mg/L and 100 mg/L treatment lines as references. The specificity of 55.3% when using the 150 mg/kg dose-estimate for predicting serum level above the 150 mg/L treatment line means 44.7% of patients may be unnecessarily treated with NAC. The ROC analysis also confirms that the dose-estimate of 150 mg/kg approximates very closely the optimal cutoff determined by the maximal Youden index. In addition, it is

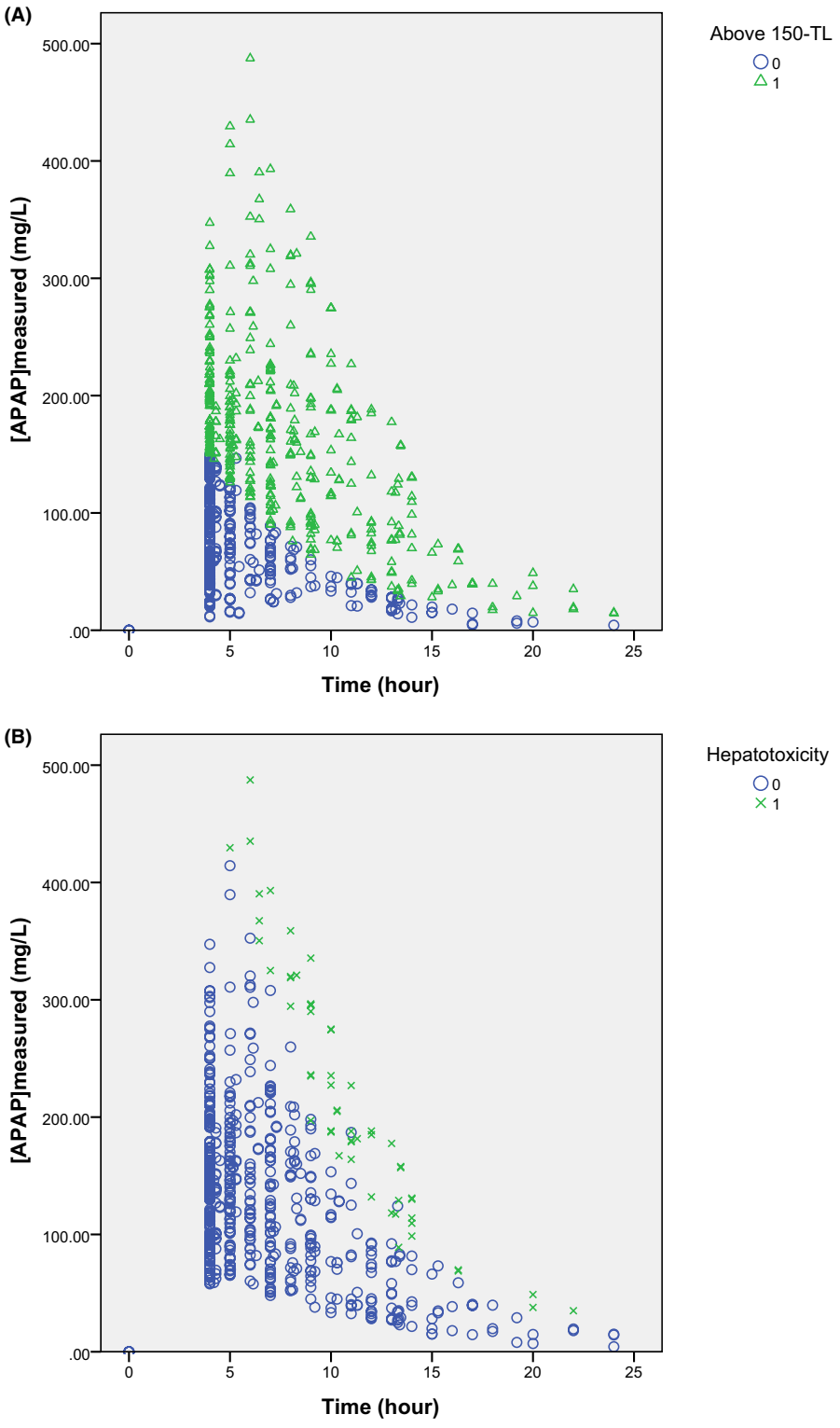

FIGURE 2 (A) Time (hours) and measured acetaminophen concentrations ([APAP]measured; unit mg/L) for the 784 analyzed cases (cases with and without acetaminophen concentrations above 150 g/L treatment line are marked in triangles and circles, respectively). (B) Time (hours) and measured acetaminophen concentrations ([APAP] measured; unit mg/L) for the 784 analyzed cases (cases with and without hepatotoxicity are marked in cross and circles, respectively)

representative of groups with and without activated charcoal decontamination. On the contrary, the dose-estimate of 200 mg/kg does not have sufficient sensitivity due to its 20.7% false negative rate when using the 150 mg/L treatment line as reference. In addition, the three patients (3.7%) whose dose-estimates fall below 200 but above 150 mg/kg and are already experiencing hepatotoxicity would have had even worse outcomes without treatment. Other dose-estimate thresholds, e.g., 8 and 10 g, have even lower sensitivity and specificity and do not fit our objective of establishing a safe dose-estimate criterion. The low specificity associated with these cutoff values in our study, undoubtedly, would lead to an increase in unnecessary NAC therapy. A significant proportion of these patients have serum acetaminophen levels that are below the 150 mg/L treatment line. Consequently, studies suggest that they are more likely to experience the adverse effects from NAC therapy that include skin rash, flushing, nausea, vomiting, and potentially

TABLE 3 Sensitivities, specificities, positive and negative predictive values and their 95% confidence intervals (in the brackets) of the cut-off doses in predicting the treatment lines

	Treatment line 150				Treatment line 100			
Dose cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
150 mg/kg	92.6 (89.6, 94.8)	55.3 (50.3, 60.2)	69.0 (65.0, 72.7)	87.4 (82.6, 91.1)	91.8 (89.2, 93.7)	89.7 (84.9, 93.1)	96.0 (94.0, 97.3)	80.3 (74.8, 84.9)
200 mg/kg	79.3 (75.1, 83.0)	62.4 (57.4, 67.2)	69.4 (65.1, 73.4)	73.8 (68.7, 78.3)	78.4 (74.9, 81.6)	92.1 (87.6, 95.0)	96.3 (94.2, 97.7)	61.6 (56.1, 66.7)
100 mg/kg	98.5 (96.8, 99.3)	17.2 (13.7, 21.3)	56.1 (52.4, 59.7)	91.5 (82.8, 96.1)	98.6 (97.3, 99.3)	29.4 (23.7, 35.9)	78.8 (75.7, 81.7)	88.7 (79.3, 94.2)
8 g	91.1 (88.0, 93.5)	35.7 (31.0, 40.7)	60.4 (56.4, 64.2)	78.9 (72.2, 84.4)	90.2 (87.5, 92.4)	53.7 (47.1, 60.3)	83.8 (80.7, 86.6)	67.3 (59.9, 73.8)
10 g	90.6 (87.4, 93.1)	39.2 (34.4, 44.2)	61.5 (57.6, 65.4)	79.6 (73.2, 84.7)	89.1 (86.3, 91.4)	57.9 (51.2, 64.4)	84.9 (81.9, 87.6)	66.7 (59.6, 73.0)
12 g	64.5 (59.8, 69.0)	71.2 (66.4, 75.5)	70.6 (65.8, 75.0)	65.1 (60.4, 69.6)	61.8 (57.7, 65.7)	91.1 (86.6, 94.2)	94.9 (92.1, 96.7)	47.2 (42.4, 52.0)

Abbreviations: NPV, negative predictive value; treatment line 150, line passing 150 mg/L at 4 h in Rumack Matthew Nomogram; treatment line 100, line passing 100 mg/L at 4 h in Rumack Matthew Nomogram; PPV, positive predictive value.

fatal anaphylactoid reactions.[21,22] Economically, the availability of the acetaminophen level has the potential to reduce overall expenditures by 14.2%.

Evidently, when obtaining a timely result of acetaminophen concentration is not feasible, using the dose-estimate cutoff of 150 mg/kg becomes a prudent alternative. Our findings also suggest that 12.6% of patients whose dose-estimate is less than 150 mg/kg may still have acetaminophen concentrations above the 150 mg/L treatment line. This reemphasizes the need for an additional follow-up of aminotransferase level at 24 h post-ingestion in all patients with dose-estimates between 100 and 149 mg/kg. The overall cumulative incidence of acute liver injury in this subgroup of patients is 7.1%. And although acute liver injury can be considered merely a biochemical change with no serious clinical impacts,[15,23] NAC therapy should still be considered, out of an abundance of caution, if the follow-up aminotransferase is ≥50 U/L.[6] In addition, our study, as well as a study by Duffull,[10] reiterates the importance of decontamination with activated charcoal since it is shown to significantly reduce the need for treatment with NAC.

The limitations of our study are consistent with its retrospective nature. The process of obtaining the ingested dose, body weight, and time of ingestion may be erratic and result in a misclassification bias. There is a potential for a sampling bias due to the significant proportion of excluded subjects at screening (39%). The incidence of hepatotoxicity among subjects who are excluded because of incomplete data such as no recorded weight, time of ingestion, or amount ingested, the incidence of hepatotoxicity is 4.2%, lower than in the study population (7.6%). This can be due to the fact that the ingestion has been judged to be non-toxic in the first place, and the treating physician does not feel the need to obtain or record related information regarding the ingestion. Along the same line, the analyzed group has a larger average ingested dose, higher acetaminophen concentrations, and a higher proportion of acetaminophen concentration ≥150 mg/L treatment line. These biases may result in an inflation of the sensitivity and underestimation of the specificity of this method. Another possible bias is a measurement bias since patients with a larger ingested acetaminophen dose and higher acetaminophen concentration have a higher tendency to be followed for liver enzymes and other markers of liver injury. This bias may result in increased rates of hepatotoxicity and acute liver injury among those with acetaminophen concentration above the 150 mg/L treatment line. However, we do not expect that the biases have any effects on the findings of ALI at average doses below 150 mg/kg. Back extrapolation using the half-life of 4 h may not accurately represent each individual patient's actual half-life, ultimately resulting in an erroneous estimation of acetaminophen concentration at 4 h for some patients. We suggest that future studies be performed which prospectively and comprehensively evaluate the accuracy of dose-estimate methods for all dose thresholds and treatment lines in the Modified Rumack-Matthew Nomogram in order to better ascertain the reliability of each dose estimation in predicting the risk of hepatotoxicity.

TABLE 4 Clinical outcomes of patients whose ingested dose are above and below 150 mg/kg

Parameter	Dose ≥150 mg/kg ($n = 545$)	Dose <150 mg/kg ($n = 239$)	Risk ratio (95% CI)	*p*-value
Acetaminophen concentration above 150-treatment line (count (%))	376 (69.0)	30 (12.6)	5.5 (3.9, 7.7)	<.001
Hepatotoxicity (count (%))	57 (10.5)	0 (0)	—	<.001
Acute liver injury (count (%))	171 (31.4)	17 (7.1)	4.4 (2.7, 7.1)	<.001

Abbreviation: CI, confidence interval.

TABLE 5 Characteristics of patient whose ingested acetaminophen dose is less than 150 mg/kg ($n = 239$) with and without acute liver injury (ALI)

	ALI ($n = 17$)	No ALI ($n = 222$)	*p*-value
Ingested dose (median (IQR)) (mg)	125.0 (108.7, 138.4)	115 (100, 134.2)	.61
Late presentation (count (%))	12 (70.6)	25 (27.5)	<.001
C4 (mg/L)	138.6 (126.5, 169.6)	84.9 (72.6, 138.8)	<.01
Activated charcoal	3 (17.6)	126 (56.8)	.001
NAC therapy	9 (52.9)	0 (0)	<.001
Initial AST (U/L)	21 (14, 41)	19 (15, 23)	.30
Initial ALT (U/L)	19 (13, 43)	18 (12, 22)	.23
Peak AST (U/L)	82 (55, 276)	26 (22, 31)	<.001
Peak ALT (U/L)	99 (58, 283)	25 (16, 34)	<.001

Abbreviations: ALI, acute liver injury; ALT, aspartate aminotransferase; AST, aspartate aminotransferase; C4, acetaminophen concentration at 4 h as derived by back extrapolation; NAC, N-acetylcysteine.

5 | CONCLUSIONS

The threshold of 150 mg/kg obtained through the dose-estimation method is a sensitive and reasonable tool in determining the need for NAC therapy. This can be extremely useful in settings where the timely analysis of acetaminophen concentration is not feasible. Application of this threshold needs to be combined with gastrointestinal decontamination with activated charcoal. An additional follow-up of liver enzymes at 24 h is recommended for those with dose estimates of 100–149 mg/kg to achieve safe and cost-effective patient management. Available acetaminophen concentration analysis reduces the cost of management by at least 14%.

DISCLOSURE

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Summon Chomchai, Pattaraporn Mekavuthikul, Jariya Phuditshinnapatra, and Chulathida Chomchai contributed to study conception, data collection and data analysis. The manuscript was written by Summon Chomchai and Chulathida Chomchai (original draft) with inputs from Pattaraporn Mekavuthikul and Jariya Phuditshinnapatra. All authors read and approved the final manuscript.

ETHICS APPROVAL STATEMENTS

The protocol is approved by Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University (project ID: 436/2564). The study is conducted in compliance with the principles outlined in the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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