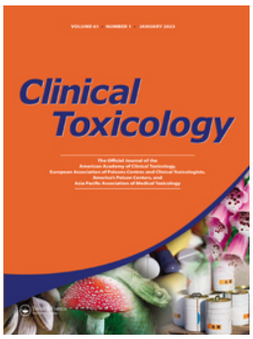

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Chun En Yau, Haoyang Chen, Bryant Po-Yuen Lim, Mingwei Ng, R. Ponampalam, Daniel Yan Zheng Lim, Yip Han Chin & Andrew Fu Wah Ho (2023) Performance of the paracetamol-aminotransferase multiplication product in risk stratification after paracetamol (acetaminophen) poisoning: a systematic review and meta-analysis, Clinical Toxicology, 61:1, 1-11, DOI: 10.1080/15563650.2022.2152350

To link to this article: https://doi.org/10.1080/15563650.2022.2152350

CLINICAL TOXICOLOGY
2023, VOL. 61, NO. 1, 1–11
https://doi.org/10.1080/15563650.2022.2152350

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REVIEW

Performance of the paracetamol-aminotransferase multiplication product in risk stratification after paracetamol (acetaminophen) poisoning: a systematic review and meta-analysis

Chun En Yau[a], Haoyang Chen[a], Bryant Po-Yuen Lim[a], Mingwei Ng[b], R. Ponampalam[b], Daniel Yan Zheng Lim[c], Yip Han Chin[a] and Andrew Fu Wah Ho[d,e]

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ABSTRACT

Background: Risk stratification in paracetamol (acetaminophen) poisoning is crucial because hepatotoxicity is common and can be mitigated with treatment. However, current risk stratification tools have limitations.

Aims: We evaluated the diagnostic performance of the paracetamol concentration × aminotransferase multiplication product, for predicting hepatotoxicity after paracetamol overdose.

Methods: Medline, Cochrane Library and Embase were searched for eligible papers. We used random effects models to obtain pooled estimates of the likelihood ratios and diagnostic odds ratios, from which sensitivity and specificity were computed. We assessed two commonly used cut-off values of paracetamol × aminotransferase, 1500 mg/L × IU/L and 10,000 mg/L × IU/L. Using the confusion matrices of these two cut-offs, area under the summary receiver operator characteristic curve and optimal cut-off values in different clinical scenarios were established.

Results: Six studies comprising 5036 participants were included. In 4051 patients, using the cut-off of 1500 mg/L × IU/L, a diagnostic odds ratio of 31.90 (95%CI: 9.52–106.90), sensitivity of 0.98 (95%CI: 0.94–1.00) and specificity of 0.66 (95%CI: 0.49–0.89) were obtained. In 3983 patients, using the cut-off of 10,000 mg/L × IU/L, a diagnostic odds ratio of 99.34 (95%CI: 12.26–804.87), sensitivity of 0.65 (95%CI: 0.51–0.82) and specificity of 0.97 (95%CI: 0.95–1.00) were obtained. For staggered ingestions, the 1500 mg/L × IU/L cut-off yielded a diagnostic odds ratio of 69.53 (95%CI: 4.03–1199.75), sensitivity of 1.00 (95%CI: 0.87–1.00) and specificity of 0.74 (95%CI: 0.43–1.00). Next, using the 10,000 mg/L × IU/L cut-off in this scenario yielded a diagnostic odds ratio of 254.58 (95%CI: 11.12–5827.60), sensitivity of 0.79 (95%CI: 0.59–1.00) and specificity of 0.98 (95%CI: 0.94–1.00). The overall summary receiver operator characteristic curve was 0.91 (95%CI: 0.75–0.97), and the optimal cut-off value was 3840 mg/L × IU/L. The summary receiver operator characteristic curve in patients with staggered ingestions was 0.96 (95%CI: 0.85–0.99). The summary receiver operator characteristic curve in patients with staggered ingestions and whose paracetamol concentration was below the detectable limit of 10 mg/L at presentation was 0.97 (95%CI: 0.94–0.99).

Conclusion: In this first meta-analysis, paracetamol × aminotransferase demonstrates its use in prognosticating hepatotoxicity in patients with paracetamol poisoning. It complements the Rumack-Matthew nomogram as it has shown promise in addressing two key limitations of the nomogram: it is usable after more than 24 h between overdose and acetylcysteine treatment, and it is applicable in staggered ingestions.

ARTICLE HISTORY
Received 11 July 2022
Revised 19 November 2022
Accepted 22 November 2022

KEYWORDS
Hepatotoxicity; acetaminophen; paracetamol; tylenol; acetylcysteine; liver injury; overdose; poisoning; risk; systematic review; meta-analysis

Introduction

Paracetamol (acetaminophen) overdose is the most common treatable cause of acute liver failure in the United States and the United Kingdom [1]. Paracetamol was estimated to cause up to 48% of acute liver failure in patients [2]. Studies have also shown an increase in incidence of paracetamol overdose cases in the past few years [3–6]. Although an effective antidote acetylcysteine exists [7], acetylcysteine is associated with high incidence of adverse drug reactions (ADR), with studies reporting ADR between 9% and 77% of patients [8]. Symptoms reported include anaphylactoid reactions, headache, dizziness and convulsion [8]. Failure to initiate acetylcysteine promptly could conversely lead to paracetamol-induced liver failure necessitating liver transplant. Acetylcysteine is also very effective when treatment starts earlier. Patients who receive treatment within the first 8 h

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2022.2152350.

after an overdose have an extremely low risk of developing hepatotoxicity [9,10], further highlighting the necessity of early identification of overdose. While there has been recent literature [11,12] highlighting treatment regimens that lower the risk of acetylcysteine-associated ADR, objective risk stratification tools are still required to prevent unnecessary acetylcysteine initiation, while minimising the risk of paracetamol-associated hepatotoxicity.

Among the most commonly used risk stratification tools recommended by international guidelines, such as the one published by the Treatment of Paracetamol Poisoning Writing Group in New Zealand and Australia [13], is the Rumack-Matthew nomogram. This nomogram estimates the risk of toxicity and guides the prognostication and treatment of acute paracetamol ingestion [14] by plotting serum paracetamol concentrations against hours since ingestion. Treatment with acetylcysteine is recommended if the "treatment line" is exceeded. However, this method suffers from several disadvantages. It is not validated for staggered ingestions or repetitive supratherapeutic [15] ingestions, delayed presentation beyond 24 h, sustained release formulations [16], and hinges on a known and reliable time of ingestion [17–19]. The decision to commence acetylcysteine is therefore often hampered by inaccurate reporting of timing of ingestion and dose ingested, especially since suicidal patients may have intentionally overdosed [20] and may not be in the correct mental state to offer reliable details about the overdose. Excessive heavy alcohol consumption can also trigger liver injury even at therapeutic doses of paracetamol [21]. Thus, in chronic alcohol abusers, the potentiation of paracetamol toxicity is not captured by the nomogram.

Newer risk stratification tools which measure the formation of reactive metabolites have emerged with increasing research into the molecular mechanisms of drug induced liver injury. These mechanistic biomarkers such as microRNA-122 and keratin-18 are slated to be more unique and applicable to the individual patient [22–24]. However, these biomarker assays are currently not routinely available in most emergency departments or medical centres. Predictors of hepatotoxicity in paracetamol overdose patients using commonly measured biochemical values are needed. One such predictor is the product of the serum paracetamol concentration and aminotransferase activity (AT), using the activity of alanine aminotransferase (ALT) or aspartate transferase (AST), whichever is higher [18]. Lower limit cut-off value paracetamol × aminotransferase = 1500 mg/L × IU/L proposed by Sivilotti et al. [25] and upper limit cut-off value paracetamol × aminotransferase = 10,000 mg/L × IU/L by Wong et al. [26] are the limits investigated by existing studies.

Patients with a paracetamol × AT above the upper limit have a high likelihood of developing hepatotoxicity, especially if it is more than 8 h post-ingestion [27]. Conversely, a product below the lower limit is associated with a low likelihood of developing hepatotoxicity [26]. Paracetamol × AT can potentially complement the Rumack-Matthew nomogram for guiding the decision to administer acetylcysteine, especially in cases of staggered ingestion, repetitive supratherapeutic ingestions or unknown time of ingestion. For example, the paracetamol × AT product can even account for unmetabolized paracetamol in the patient at the time of presentation [18,28]. However, there have been few large-scale studies and no meta-analysis to evaluate the diagnostic utility of paracetamol × AT.

Aims

We evaluated the diagnostic performance of the paracetamol concentration × aminotransferase multiplication product, for predicting hepatotoxicity after paracetamol overdose.

Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this systematic review and meta-analysis [29]. We accessed Medline, Cochrane Library and Embase to identify relevant papers from database inception to 23 November 2021, with language restricted to English. A search strategy was developed in conjunction with content experts using keywords and MeSH terms synonymous to "alanine transaminase," "aspartate transaminase," "acetaminophen," "multiplication," "liver injury," "hepatotoxicity," "prediction," "prognostic" were utilized. Three authors independently carried out the preliminary eligibility screening in a blinded fashion. The authors screened the titles and abstracts before retrieving and reviewing the full texts. Reviews, letters, comments, animal studies, case reports and papers which solely investigated paediatric populations were excluded. Conference abstracts which published sufficient data to create confusion matrices were included due to the small number of studies in this field. A senior author resolved differences by discussion and consensus. Studies were included if they (1) included any mention of paracetamol overdose/poisoning/toxicity and (2) utilised paracetamol × AT.

Data extraction and selection criteria

From each study, we used a standardised data extraction sheet to extract information on the study period, country, population demographics and acetylcysteine treatment procedures by two authors independently. Paracetamol × AT was defined as the product of the first recorded values of simultaneously measured serum paracetamol concentration and either ALT or AST activity (whichever is higher). Hepatotoxicity was defined as peak ALT or AST more than 1000 IU/L [26–28,30–32].

Statistical analysis

All analysis was done using RStudio (version 2021.9.1.372). Statistical analysis was conducted with the *mada* (version 0.5.10), *meta* (version 5.2–0) and *diagmeta* (version 0.5–0) packages. Meta-analyses of proportions were conducted using *meta* to estimate overall prevalence of hepatotoxicity

in included study populations, and to pool log-transformed sensitivity and specificity for the two limits. Using *mada*, random effects model following the DerSimonian and Laird approach was used to pool the data to obtain overall negative likelihood ratio (LR−), positive likelihood ratio (LR+), diagnostic odds ratio (DOR) of the two limits [33]. Due to the small number of studies, the univariate approach was used in the calculation of DOR, LR- and LR+. Heterogeneity was measured using I^2 values [34]. Using *diagmeta* which utilises the approach outlined by Steinhauser et al. [35], different linear mixed models were fitted to estimate the distribution function of paracetamol × AT within the included studies. For the linear mixed models that converged, we applied the restricted maximum likelihood criterion and the model that minimised this criterion was selected. An overall summary receiver operator characteristic (sROC) curve and the area under this sROC curve (AUC) were derived for different clinical scenarios. For each scenario, the optimum cut-off value was calculated. The optimum cut-off value is the cut-off where the maximum of a weighted sum of sensitivity and specificity is obtained.

Subgroup analysis of factors that might alter paracetamol × AT's prognostic utility was conducted where possible. Subgroups include nature of ingestions (single or staggered), timing between ingestion and overdose, the use of paracetamol × AT in predicting acute liver injury and use of paracetamol × AT when the paracetamol concentration was below the detectable limit of 10 mg/L at presentation.

Risk of bias assessment

Two independent and blinded authors assessed studies for methodological quality, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [36] for diagnostic studies. The QUADAS-2 tool assesses the quality of studies across four key domains: patient selection, index test, reference standard and flow and timing. Disagreements were resolved through discussion with a third independent author.

Results

The search strategy identified 564 relevant studies (Figure 1). 496 studies were left after removal of duplicates, of which 24 studies were included in the full-text review. Ultimately, four studies and two conference abstracts were included in this review, comprising 5036 patients (Figure 1). Of these six studies, two were from Australia [28,30], two were from the USA [31,32], one was from the United Kingdom [26] and one was from Thailand [27]. The population demographic characteristics were reported in Table 1. Two studies used only the lower limit of 1500 mg/L × IU/L, one study used the upper limit of 10,000 mg/L × IU/L, and three studies examined both cut-off values. All are retrospective studies. All patients in three studies [27,28,32] received acetylcysteine treatment, while in three studies, a portion of the patients received acetylcysteine [26,30,31]. All studies were at low risk of bias (Supplementary Figure 1).

Incidence of hepatotoxic events

In the pooled analysis of 4051 patients across the five studies [26–28,30,31] which investigated the lower limit, the prevalence of hepatotoxicity was 3.99% (95%CI: 0.98–14.79%). In the pooled analysis of 3983 patients across the four studies [26,28,30,32] which investigated the upper limit, the overall prevalence of hepatotoxicity was 4.19% (95%CI: 0.68–21.80%).

Overall diagnostic accuracy of paracetamol × aminotransferase

Using the lower limit as the cut-off to prognosticate if a patient will develop hepatotoxicity yielded a DOR of 31.90 (95%CI: 9.52–106.90), sensitivity of 0.98 (95%CI: 0.94–1.00) and specificity of 0.66 (95%CI: 0.49–0.89) (Figure 2). A summary of the analysis can be seen in Table 2. Using the upper limit as the cut-off to prognosticate if a patient will develop hepatotoxicity yielded a DOR of 99.34 (95%CI: 12.26–804.87), sensitivity of 0.65 (95%CI: 0.51–0.82) and specificity of 0.97 (95%CI: 0.95–1.00) (Figure 3). The overall AUC value (Figure 4) of using paracetamol × AT is 0.91 (95%CI: 0.75–0.97), and the overall optimal cut-off value of paracetamol × AT is 3840 mg/L × IU/L. At this cut-off, sensitivity is 0.81 (95%CI: 0.58–0.93) and specificity is 0.91 (95%CI: 0.78–0.97).

Diagnostic accuracy of paracetamol with varied ingestion types

Further subgroup analysis was conducted on the types of ingestion. Using the lower limit to prognosticate hepatotoxicity following single ingestions yielded a DOR of 70.88 (95%CI: 5.27–952.69), sensitivity of 1.00 (95%CI: 0.94–1.00) and specificity of 0.57 (95%CI: 0.22–1.00). When using the upper limit, single ingestion yielded a DOR of 272.71 (95%CI: 12.91–5761.54), sensitivity of 0.73 (95%CI: 0.52–1.00) and specificity of 0.99 (95%CI: 0.97–1.00). The AUC value of paracetamol × AT calculated for the subgroup of patients who had single ingestions was 0.96 (95%CI: 0.90–0.99), and the optimal cut-off value was 3730 mg/L × IU/L. At this cut-off, sensitivity is 0.90 (95%CI: 0.76–0.96) and specificity is 0.94 (95%CI: 0.59–0.99).

Prognosticating hepatotoxicity in staggered ingestions using the lower limit yielded a DOR of 69.53 (95%CI: 4.03–1199.75), sensitivity of 1.00 (95%CI: 0.87–1.00) and specificity of 0.74 (95%CI: 0.43–1.00). Prognosticating hepatotoxicity in staggered ingestions using the upper limit yielded a DOR of 254.58 (95%CI: 11.12–5827.60), sensitivity of 0.79 (95%CI:0.59–1.00) and specificity of 0.98 (95%CI: 0.94–1.00). The AUC value of paracetamol × AT calculated for the subgroup of patients who ingested paracetamol in a staggered manner was 0.96 (95%CI: 0.85–0.99), and the optimal cut-off value was 3140 mg/L × IU/L. At this cut-off, sensitivity is 0.88 (95%CI: 0.64–0.97) and specificity is 0.94 (95%CI: 0.42–1.00).

Prognosticating hepatotoxicity using the lower limit in staggered ingestion (secondary analysis, where serum paracetamol concentration was below the detectable limit of 10 mg/L and a value of the paracetamol concentration = 5 mg/L was substituted into paracetamol × AT) yielded a

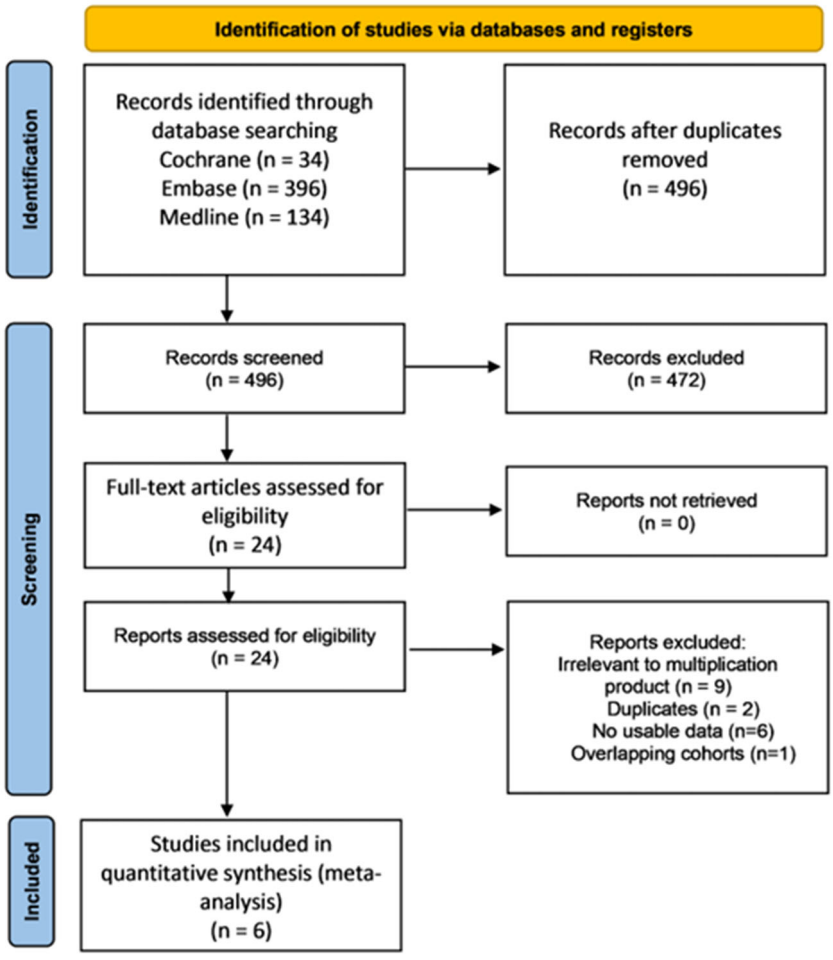

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

DOR of 145.55 (95%CI: 14.25–1486.92), sensitivity of 1.00 (95%CI: 0.77–1.00) and specificity of 0.97 (95%CI: 0.93–1.00). At the upper limit, staggered ingestion (secondary analysis) prognostication yielded a DOR of 59.47 (95%CI: 5.49–643.81), sensitivity of 0.45 (95%CI: 0.19–1.00) and specificity of 1.00 (95%CI: 0.97–1.00). The AUC value of paracetamol × AT calculated for the subgroup of patients who ingested paracetamol in a staggered manner (secondary analysis) was 0.97 (95%CI: 0.94–0.99), and the optimal cut-off value was 722 mg/L × IU/L. At this cut-off, sensitivity is 0.95 (95%CI: 0.80–0.99) and specificity is 0.92 (95%CI: 0.70–0.98).

Timing of ingestion

Using the lower limit to prognosticate for hepatotoxicity in patients receiving treatment more than 8 h after ingestion yielded a DOR of 85.37 (95%CI: 25.97–280.58), sensitivity of 0.96 (95%CI: 0.87–1.00) and specificity of 0.74 (95%CI: 0.47–1.00). Using the upper limit to prognosticate for hepatotoxicity in patients receiving treatment within 8 h of ingestion yielded a DOR of 367.17 (95%CI: 33.95–3971.24), sensitivity of 0.81 (95%CI: 0.60–1.00) and specificity of 0.98 (95%CI: 0.95–1.00). No meta-analysis was conducted for treatment after more than 8 h since ingestion for the upper limit as there was only one study [28].

Discussion

Early identification, prognostication and treatment of paracetamol overdose patients is vital as acetylcysteine significantly reduces the risk of the patient developing serious hepatotoxicity if the patient receives it less than 8 h after ingestion [37]. This is important as patients who do not receive acetylcysteine in time will cause the treatment to be less efficacious and they might eventually develop acute liver failure, for which the definitive treatment is liver transplant [38]. In this paper, we have demonstrated the high DORs of using paracetamol × AT cut-off values of 1500 mg/L × IU/L and 10,000 mg/L × IU/L. Given the debilitating effects of liver failure, and the comparatively mild adverse side effects of acetylcysteine treatment, the high sensitivity of paracetamol × AT at the lower limit is noteworthy, as it will accurately identify a vast majority of the true positive cases amongst those who will eventually develop hepatotoxicity. We have also shown the potential of using paracetamol × AT in patients who ingested paracetamol in a staggered manner or patients with unknown time of ingestion of paracetamol, the two main shortcomings of the nomogram. Summary ROC analysis showed high sensitivity and specificity in prognosticating hepatotoxicity in these two settings. Though the utility of this result is limited by the small sample size and the variable acetylcysteine treatment, it hints at the great

Table 1. Baseline characteristics.

Author (year)	Location	Study period	Study design	*n*	Age (year) Mean ± *SD*	Male (%)	Acetaminophen ingestion characteristics Median (IQR)	Treatment regimen	Limits investigated and number of patients exceeding the limit	Definition of hepatotoxicity	Outcomes
Egan et al.[30]	Australia	3Jan 2012–Jun 2017	Retrospective cohort study	266	43.0 ± 19.4	45.5	9 g per 24 h (6–12 g) Thirty-one (12%) patients took modified release paracetamol 9 had combination abuse together with paracetamol	139 received NAC, of which 64 received an abbreviated course (unspecified if 2 or 3 bag NAC treatment).	APAP × *AT* > 1500 mg/L × IU/L (58) APAP × *AT* > 10,000 mg/L × IU/L (13)	*ALT* > 1000 U/L	Primary: • Develop HT – *ALT* > 1000 U/L (17) Secondary • Death (2 in total. 1 unrelated to paracetamol while the other had multi-factorial causes) • Liver transplant (0) • Acute Liver Injury – *ALT* ≥ 50 U/L (94; 89 already presented with *ALT* ≥ 50, 5 more developed subsequently)
Wong et al.[28]	Australia	Feb 2014–Aug 2016	Retrospective cohort study	447	29.4 ± 19.0	23.3	HT: 254 mg/kg (140–366) Non-HT: 225 mg/kg (167–333)	All 447 patients received a two-bag NAC regimen — 200 mg/kg fused over 4 h followed by a further 100 mg/kg infused over 16 h	APAP × *ALT* > 1500 mg/L × IU/L (248) APAP × *ALT* > 10,000 mg/L × IU/L (26)	*ALT* ≥ 1000 IU/L	Primary: • Develop HT – *ALT* ≥ 1000 U/L (5) Secondary • Acute Liver Injury – peak *ALT* ≥ 2× baseline ALT & above 50 IU/L (13) • No deaths or transplants
Nacca et al.[31]	USA	Jul 2011–Jul 2014	Retrospective cohort study	29	–	–	Staggered, chronic & time unknown APAP overdoses	17 out of 18 patients who had acute, known timing of ingestion received NAC therapy. 11 patients who had staggered, chronic & time unknown APAP overdose did not receive NAC therapy.	APAP × *AT* > 1500 mg/L × IU/L (11)	*AST* ≥ 1000 IU/L	Primary: • Develop HT – *AST* ≥ 1000 U/L (1) • No deaths or transplants
Wong et al.[26]	UK	Feb 2005–Mar 2013	Retrospective cohort study	3823	30.0 ± 5.90	41.5	All patients with APAP overdose and both serum APAP & ALT activity measured	1304 patients received IV NAC therapy; of which all 34 patients with HT received the entire 300 mg/kg UK NAC regimen	APAP × *ALT* > 1500 mg/L × IU/L (281) APAP × *ALT* > 10,000 mg/L × IU/L (26)	*ALT* > 1000 U/L	Primary: • Develop HT – *ALT* > 1000 U/L (20) Secondary: • Coagulopathy – peak *INR* > 2 (unclear in paper) • No transplants • 2 deaths (Both unrelated to paracetamol)

(*continued*)

Table 1. Continued.

Author (year)	Location	Study period	Study design	*n*	Age (year) Mean ± *SD*	Male (%)	Acetaminophen ingestion characteristics Median (IQR)	Treatment regimen	Limits investigated and number of patients exceeding the limit	Definition of hepatotoxicity	Outcomes
Chomchai et al.[27]	Thailand	Jan 2004–Jun 2012	Retrospective cohort study	255	23.0 ± 5.90	15.7	Acute isolated APAP overdose presenting within 24 h of ingestion	All 255 patients received standard NAC therapy	APAP × AT > 1500 mg/L × IU/L (112)	AT ≥ 1000 IU/L	Primary: • Develop HT – AT ≥ 1000 U/L (32) Secondary: • Coagulopathy – peak INR > 2 (169) • No fulminant liver failure or deaths • Transplants not indicated
Offerman et al.[32]	USA	Jul 2003–Dec 2007	Retrospective cohort study	216	–	25.5	Acute, isolated APAP overdose presenting within 24 h of ingestion	All 216 patients received NAC therapy	APAP × AT > 10,000 mg/L × IU/L (27)	AT ≥ 1000 IU/L	Primary: • Develop HT – AST or ALT ≥ 1000 U/L (27) • No deaths or transplants

Legend.
ALT: Alanine transaminase.
APAP: Acetaminophen.
AST: Aspartate aminotransferase.
AT: Aminotransferase.
HT: Hepatotoxic.
INR: International normalised ratio.
IQR: interquartile range.
NAC: N-acetylcysteine.
All values are presented as mean ± standard deviation or median (IQR).

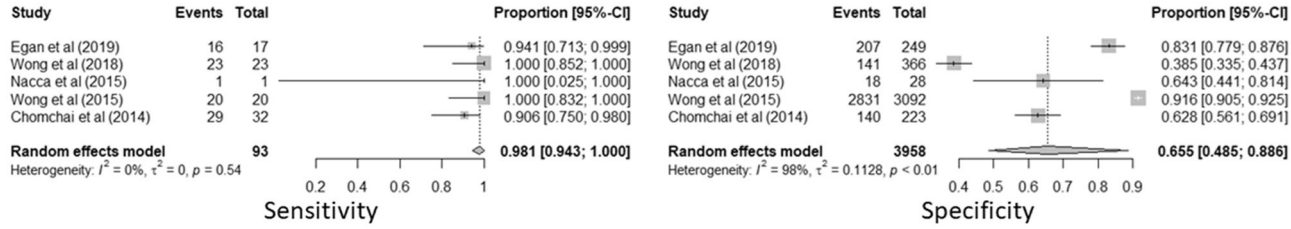

Figure 2. Sensitivity and specificity for 1500 mg/L × IU/L limit.

Table 2. Summary of overall analyses.

	Number of studies	*n*	DOR	95% CI	I^2	LR+	95% CI	I^2	LR−	95% CI	I^2
Overall											
1500 mg/L × IU/L	5	4051	31.90	9.52–106.90	5.26%	3.51	1.31–9.40	0.00%	0.13	0.06–0.27	0.00%
10,000 mg/L × IU/L	4	3983	99.34	12.26–804.87	0.00%	35.99	6.28–206.20	0.00%	0.39	0.25–0.62	0.00%
Subgroup analyses											
1500 mg/L × IU/L (Single ingestion)	2	3063	70.88	5.27–952.69	0.00%	4.10	0.57–29.60	0.00%	0.06	0.01–0.40	0.00%
10,000 mg/L × IU/L (Single ingestion)	2	3063	272.71	12.91–5761.54	0.00%	77.25	9.03–660.73	0.00%	0.32	0.14–0.73	0.00%
1500 mg/L × IU/L (Staggered ingestion)	2	438	69.53	4.03–1199.75	0.00%	6.32	0.71–56.38	0.00%	0.09	0.01–0.61	0.00%
10,000 mg/L × IU/L (Staggered ingestion)	2	438	254.58	11.12–5827.60	0.00%	66.22	2.12–2072.04	0.00%	0.28	0.12–0.64	0.00%
1500 mg/L × IU/L (Staggered ingestion, secondary analysis)	2	82	145.55	14.25–1486.92	0.00%	15.96	5.96–42.71	0.00%	0.12	0.02–0.75	0.00%
10,000 mg/L × IU/L (Staggered ingestion, secondary analysis)	2	82	59.47	5.49–643.81	0.00%	33.52	4.14–271.33	0.00%	0.58	0.32–1.02	0.00%
1500 mg/L × IU/L (Within 8 h of ingestion)	2	290	0.61	0.05–7.38	0.00%	0.89	0.42–1.87	0.00%	1.40	0.30–6.47	0.00%
1500 mg/L × IU/L (After 8 h of ingestion)	2	285	85.37	25.97–280.58	0.00%	4.94	1.05–23.30	0.00%	0.11	0.04–0.27	0.00%
10,000 mg/L × IU/L (Within 8 h of ingestion)	2	2876	367.17	33.95–3971.24	0.00%	60.68	5.57–661.54	0.00%	0.23	0.09–0.63	0.00%

	Number of studies	*n*	Sensitivity	95% CI	I^2	Specificity	95% CI	I^2
Overall								
1500 mg/L × IU/L	5	4051	0.98	0.94–1.00	0.00%	0.66	0.49–0.89	98.30%
10,000 mg/L × IU/L	4	3983	0.65	0.51–0.82	54.20%	0.97	0.95–1.00	86.80%
Subgroup analyses								
1500 mg/L × IU/L (Single ingestion)	2	3063	1.00	0.94–1.00	0.00%	0.57	0.22–1.00	99.30%
10,000 mg/L × IU/L (Single ingestion)	2	3063	0.73	0.52–1.00	52.30%	0.99	0.97–1.00	79.60%
1500 mg/L × IU/L (Staggered ingestion)	2	438	1.00	0.87–1.00	0.00%	0.74	0.43–1.00	95.60%
10,000 mg/L × IU/L (Staggered ingestion)	2	438	0.79	0.59–1.00	0.00%	0.98	0.94–1.00	66.50%
1500 mg/L × IU/L (Staggered ingestion, secondary analysis)	2	82	1.00	0.77–1.00	0.00%	0.97	0.93–1.00	0.00%
10,000 mg/L × IU/L (Staggered ingestion, secondary analysis)	2	82	0.45	0.19–1.00	0.00%	1.00	0.97–1.00	0.00%
1500 mg/L × IU/L (After 8 h of ingestion)	2	285	0.96	0.87–1.00	47.10%	0.74	0.47–1.00	97.10%
10,000 mg/L × IU/L (Within 8 h of ingestion)	2	2876	0.81	0.60–1.00	0.00%	0.98	0.95–1.00	82.70%

	AUC value	95% CI	Optimal cut-off value/ mg/L × IU/L	Sensitivity at this cut-off	95% CI	Specificity at this cut-off	95% CI
Overall	0.91	0.75–0.97	3840	0.81	0.58–0.93	0.91	0.78–0.97
Subgroup analyses							
Staggered ingestion	0.96	0.85–0.99	3140	0.88	0.64–0.97	0.94	0.42–1.00
Staggered ingestion (secondary analysis)	0.97	0.94–0.99	722	0.95	0.80–0.99	0.92	0.70–0.98
Single ingestion	0.96	0.90–0.99	3730	0.90	0.76–0.96	0.94	0.59–0.99

Legend.
DOR: Diagnostic odds ratio.
95%CI: 95% Confidence intervals.
I^2: Higgins' statistic.
LR+: Positive likelihood ratio.
LR−: Negative likelihood ratio.
AUC: Area under curve value.

usefulness of paracetamol × AT, possibly complementing the nomogram in scenarios where the nomogram is not validated.

In the seminal study by Smilkstein et al. [39], amongst those treated within 8 h with oral acetylcysteine, hepatotoxicity developed in three of 214 patients whose initial paracetamol concentration was below the treatment line of the Rumack-Matthew nomogram. Using the data from Smilkstein et al.'s paper, we obtained a sensitivity of 0.83, specificity of 0.30, LR + of 1.19, LR − of 0.562 and a DOR of 2.11. Comparing this to the diagnostic utility of paracetamol × AT in patients treated within 8 h with acetylcysteine (Table 2), the DOR when using the lower limit [27,28] is much lower than that of the nomogram, but the DOR when using the upper limit [26,28] is much higher. While the utility of this finding is limited by the small number of studies included in the subgroup analysis, the high DOR of the 10,000 mg/L × IU/L certainly warrants further research. Using the data

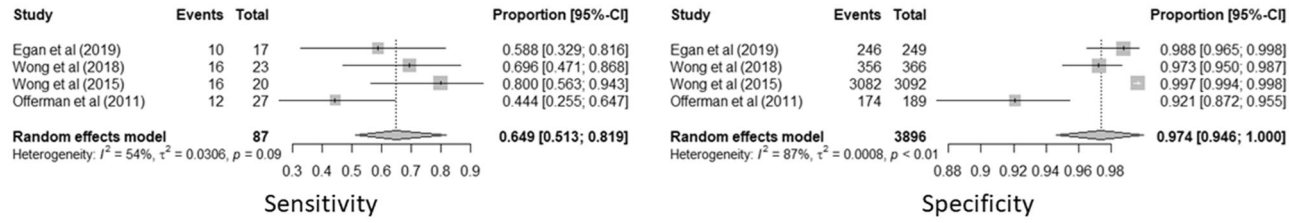

Figure 3. Sensitivity and specificity for 10,000 mg/L × IU/L limit.

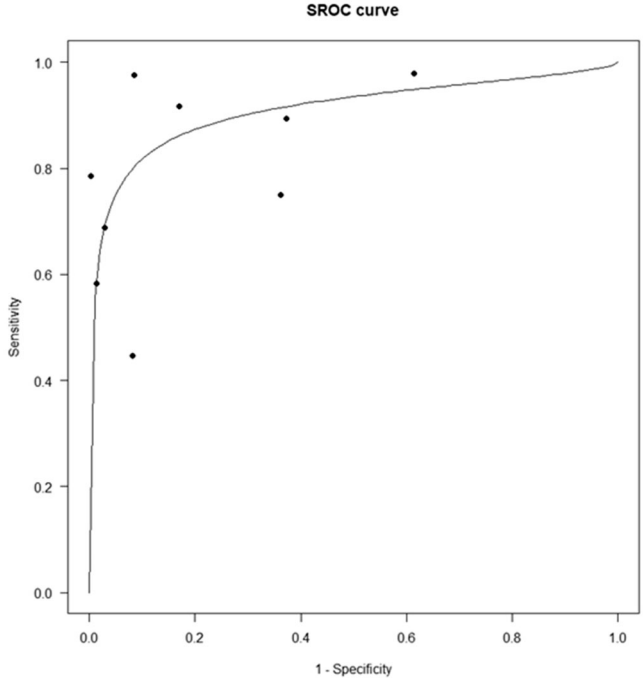

Figure 4. Summary Receiver Operating Characteristics curve for overall multiplication product (AUC: 0.91 (95% CI 0.75–0.97)).

from Prescott et al. [10], we obtained an overall sensitivity of 0.90, specificity of 0.50, positive likelihood ratio of 1.80, negative likelihood ratio of 0.20 and a diagnostic odds ratio of 9.00 for the subset of patients who were above the treatment line 300 mg/L at 4 h post overdose and received treatment 10–24 h since ingestion. While this comparison is limited by the fact that the treatment line in the included studies is not 300 mg/L, the fact that the 1500 mg/L × IU/L cut-off outperforms the 300 mg/L treatment line in the subgroup of patients who received treatment more than 8 h after ingestion warrants further research.

Our study has shown that paracetamol × AT is a potent diagnostic tool in staggered ingestions. The current gold standard for risk stratification, the nomogram, is highly challenging [28] and has not been validated in patients with staggered ingestions or delayed presentations. Our findings show that using paracetamol × AT of acute and staggered ingestions are comparable (Table 2). The significant AUC value (0.96; 95%CI: 0.85–0.99) for staggered ingestions, along with the high DOR, LR + and low LR − imply that paracetamol × AT is worthy of more investigation in this subgroup of patients. This is important as these undetected patients represent a large proportion of patients that present with signs of liver damage. In a cohort study by Leventhal et al. [40], more than half of the patients who presented with paracetamol-induced acute liver failure or injury had undetectable concentrations of paracetamol. Our study has shown that in cases where serum paracetamol concentrations are below the detectable limit of 10 mg/L, paracetamol × AT performs with high diagnostic accuracy. With a significant proportion of cases of paracetamol toxicity being due to staggered ingestions (11.1–23.5%) [18,26,28], the potential for the use of paracetamol × AT to prognosticate hepatotoxicity is significant.

Importantly, this paper has estimated different cut-off values for paracetamol × AT in different clinical settings that maximise diagnostic accuracy. The estimated cut-off value of 3840 mg/L × IU/L to predict hepatotoxicity in paracetamol overdose patients has high sensitivity and specificity. This is supported by Wong et al. [28], which showed that departure from 100% sensitivity occurs at cut-off values of more than 1500 mg/L × IU/L.

One possible area for further research is the utility of paracetamol × AT in cases where there are more than 24 h between ingestion and acetylcysteine treatment. The nomogram has only been validated for paracetamol overdose cases presenting within 24 h [39]. Only one included study [26] examined the diagnostic utility of paracetamol × AT in such cases. Paracetamol × AT demonstrates high sensitivity and specificity at both the upper and lower limits of the cut-off values. Though the conclusion of this study is limited by the small sample size, the high sensitivity and specificity, especially in scenarios where the nomogram is not validated, warrants further research.

However, we note some limitations of the current paracetamol × AT multiplication product. It should be cautioned that, in concordance with the findings of Chomchai et al. [27] and Wong et al. [18], the diagnostic value of paracetamol × AT is lower if calculated within 8 h of ingestion. An elevated paracetamol × AT within 8 h of overdose is more probably due to unmetabolized paracetamol rather than increased activities of aminotransferase [18]. In this subgroup analysis [27,28], most of the patients whose paracetamol × AT were measured within 8 h of overdose and had a paracetamol × AT of more than 1500 mg/L × IU/L were started on acetylcysteine treatment earlier. This is a confounding factor in predicting hepatotoxicity as the number of false positives will increase. Hence, in line with the suggestion of Wong et al. [18], it would be wise to repeat the paracetamol × AT calculations after certain time intervals to adjust the acetylcysteine regimen accordingly. Further studies could look at the utility of paracetamol × AT for risk

prognostication for liver failure or mortality. The multiplication product is assessed to be useful in the setting of staggered ingestions and following newer two-bag acetylcysteine regimens [28] for paracetamol overdose.

Applying the paracetamol × AT in a clinical setting, a guideline can be created according to the cut-off values investigated in this study. As more studies are conducted on the multiplication product, the overall optimal cut-off value could be updated from the estimated 3840 mg/L × IU/L as reflected in this study. Once an updated cut-off value is established, patients with paracetamol × AT above that cut-off value could be marked out as "high risk" patients and could be admitted for close monitoring. A high acetylcysteine dose and aggressive treatment can be considered in these patients. Patients below this cut-off can be marked as "low-risk," and if below 1500 mg/L × IU/L, are unlikely to develop hepatotoxicity and acetylcysteine treatment could be abbreviated or terminated.

As a caveat, it is important to note that the optimal cut-off value is defined mathematically here as the weighted sum of sensitivity and specificity. In this study, we gave equal weight to both sensitivity and specificity. However, in a clinical setting, this might not be favoured. For example, in the emergency department, sensitivity might be prioritised. In such cases, the optimal cut-off value for the multiplication product can be easily adjusted using *diagmeta* to assign more weight to sensitivity. On the flipside, if future studies were to trial newer, more intensive treatment regimens for paracetamol poisoning, it might be favourable to assign more weight to specificity. Thus, the paracetamol × AT product, along with the methods outlined in this paper, allow researchers to test out different hypotheses in different contexts.

In recent years, it has been shown that biomarkers such as microRNA-122 and keratin-18 have high specificity when prognosticating the development of acute liver injury [24]. More work should be done to validate the cost-effectiveness of incorporating these biomarkers into diagnostic algorithms. Future prospective studies should compare the diagnostic performance of the multiplication product and these biomarkers against the nomogram directly.

Strengths and limitations

This meta-analysis is the first to aggregate the data of all known studies about the paracetamol × AT multiplication product. The results provide information about the prognostic performance of the two well-established cut-off values of 1500 mg/L × IU/L and 10,000 mg/L × IU/L and provides a comprehensive overview of possible subgroups. It also presents optimal cut-off values for paracetamol × AT in different clinical scenarios where the nomogram cannot be used. Although there were no deaths or cases of acute liver failure reported in this study, this could be due to insufficient follow up time. There are reports of mortality and liver transplant in patients who have survived paracetamol poisoning in the longer term [41]. Using paracetamol × AT can help to identify more patients to undergo acetylcysteine treatment, which might hence have longer term benefits. Paracetamol × AT also accounts for many factors such as the time of ingestion, quantity of ingestion, and severity of ingestion into a single continuously valued variable, thus recognising the spectrum of severity in paracetamol poisoning unlike the Rumack-Matthew nomogram which only indicates two categories: high-risk and low-risk. It should be noted that other existent risk stratification tools, such as the King's College criteria [42], are used to predict patients with fulminant hepatic failure who will benefit from liver transplantation. In paracetamol-overdose patients, the multiplication product can be used at an early stage of treatment to adjust acetylcysteine dosage accordingly, possibly complementing the use of the King's College criteria.

However, the reliability of this study is affected by the small number of included articles ($n = 6$). There is also a relatively large range in the mean age of the patients included in the study, ranging from 29 [28] to 43 [30]. It is known that ADR incidence increases with increasing age [43]. Thus, aging could have predisposed older patients to increased hepatotoxicity risk. Amongst the studies, there was no direct comparison between paracetamol × AT and the Rumack-Matthew nomogram, so it is uncertain how many patients would have received treatment if the nomogram criteria was applied. Studies also did not mention any pre-existing liver pathological conditions or any alcoholic behaviour which would have increased the risk of hepatotoxicity for the same dosage of paracetamol. The reliability of the findings could also be affected by the inconsistent selection of patients undergoing acetylcysteine treatment, with some studies providing acetylcysteine treatment to all patients and some providing abbreviated acetylcysteine treatments or only to a portion of patients. Different studies also utilised different acetylcysteine regimens, with some administering the "traditional" three-bag acetylcysteine infusion [26,27], and others administering a two-bag regimen [28]. These could account for heterogeneity in the studies' findings. There is also a paucity of data concerning non-biochemical outcomes, such as mortality or the number of patients who required liver transplant. In future large-scale studies, it would be advisable to follow a unified guideline and regimen for acetylcysteine treatment [17,37].

In the secondary analyses included in this paper, paracetamol concentration = 5 mg/L was substituted into paracetamol × AT for overdoses with unknown paracetamol concentration. More studies can be done to validate this substituted value. This study is also limited by the lack of individual patient data. This necessitated the estimation of the AUC values and the optimal cut-off values for each subgroup of patients using the *diagmeta* package. This also prevents more granular analysis such as for example, an analysis of subgroups of patients stratified according to their presenting aminotransferase concentration and an investigation of how that affects diagnostic accuracy of paracetamol × AT. This lack of individual patient data prevented us from confirming the underlying distributions of paracetamol × AT within the study populations. This study is also limited by possible incorporation bias [18,27] as paracetamol × AT includes

aminotransferase activity. Thus, if aminotransferase activity is already more than 1000 IU/L, hence meeting the definition of hepatotoxicity, paracetamol × AT will naturally be higher. However, in such instances, paracetamol × AT can still be useful, as it provides a measure of unmetabolized paracetamol, which is a sign of impending liver injury [18]. Thus, when incorporated into a single product with aminotransferase activity, it is more useful than examining aminotransferase activity in isolation. Future work can investigate how the removal of the subgroup of patients with presenting aminotransferase activity >1000 IU/L affects the prognostic value of paracetamol × AT.

Conclusion

In conclusion, this first meta-analysis on the paracetamol × AT multiplication product demonstrates its use in prognosticating hepatotoxicity in patients with paracetamol poisoning. It complements the Rumack-Matthew nomogram as it has shown promise in addressing two key limitations of the nomogram: it is usable after more than 24 h between overdose and acetylcysteine treatment, and it is applicable in staggered ingestions.

Acknowledgements

Chun En Yau, Haoyang Chen, Bryant Po-Yuen Lim, Mingwei Ng, R. Ponampalam, Daniel Yan Zheng Lim, Yip Han Chin and Andrew Fu Wah Ho contributed to (1) the conception and design of this project; (2) acquisition, analysis, and interpretation of data; (3) drafting and revising the manuscript. All authors gave their final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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References

[1] Castaldo ET, Chari RS. Liver transplantation for acute hepatic failure. HPB (Oxford). 2006;8(1):29–34.
[2] Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42(6):1364–1372.
[3] Yoon E, Babar A, Choudhary M, et al. Acetaminophen-induced hepatotoxicity: a comprehensive update. J Clin Transl Hepatol. 2016;4(2):131–142.
[4] Tong HY, Medrano N, Borobia AM, et al. Hepatotoxicity induced by acute and chronic paracetamol overdose in adults. Where do we stand? Regul Toxicol Pharmacol. 2015;72(2):370–378.
[5] Lee WM. Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away? J Hepatol. 2017;67(6):1324–1331.
[6] Ayonrinde OT, Phelps GJ, Hurley JC, et al. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. Intern Med J. 2005;35(11):655–660.
[7] Woolum JA, Hays WB, Patel KH. Use of fomepizole, n-acetylcysteine, and hemodialysis for massive acetaminophen overdose. Am J Emerg Med. 2020;38(3):692.e5-692–e7.
[8] Koppen A, van Riel A, de Vries I, et al. Recommendations for the paracetamol treatment nomogram and side effects of N-acetylcysteine. Neth J Med. 2014;72(5):251–257.
[9] Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin. 2012;28(4):499–516.
[10] Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. Br Med J. 1979;2(6198):1097–1100.
[11] Wong A, Isbister G, McNulty R, et al. Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study). eClinicalMedicine. 2020;20:100288.
[12] Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet. 2014;383(9918):697–704.
[13] Chiew AL, Reith D, Pomerleau A, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020;212(4):175–183.
[14] Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics. 1975;55(6):871–876.
[15] Bond GR, Wiegand CB, Hite LK. The difficulty of risk assessment for hepatic injury associated with supra-therapeutic acetaminophen use. Vet Hum Toxicol. 2003;45(3):150–153.
[16] Cetaruk EW, Dart RC, Hurlbut KM, et al. Tylenol extended relief overdose. Ann Emerg Med. 1997;30(1):104–108.
[17] Dart RC, Erdman AR, Olson KR, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2006;44(1):1–18.
[18] Wong A, Sivilotti MLA, Graudins A. Accuracy of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity in modified-release paracetamol overdose. Clin Toxicol (Phila). 2017;55(5):346–351.
[19] Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40(1):3–20.
[20] Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav. 2000;30(4):313–326.
[21] Louvet A, Ntandja Wandji LC, Lemaître E, et al. Acute liver injury with therapeutic doses of acetaminophen: a prospective study. Hepatology. 2021;73(5):1945–1955.
[22] McGill MR, Jaeschke H. Mechanistic biomarkers in acetaminophen-induced hepatotoxicity and acute liver failure: from preclinical models to patients. Expert Opin Drug Metab Toxicol. 2014;10(7):1005–1017.
[23] McGill MR, Staggs VS, Sharpe MR, et al. Serum mitochondrial biomarkers and damage-associated molecular patterns are higher in acetaminophen overdose patients with poor outcome. Hepatology. 2014;60(4):1336–1345.
[24] Dear JW, Clarke JI, Francis B, et al. Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies. Lancet Gastroenterol Hepatol. 2018;3(2):104–113.
[25] Sivilotti MLA, Green TJ, Langmann C, et al. Multiplying the serum aminotransferase by the acetaminophen concentration to predict toxicity following overdose. Clin Toxicol (Phila). 2010;48(8):793–799.
[26] Wong A, Sivilotti MLA, Dargan PI, et al. External validation of the paracetamol-aminotransferase multiplication product to predict

hepatotoxicity from paracetamol overdose. Clin Toxicol (Phila). 2015;53(8):807–814.
[27] Chomchai S, Chomchai C. Predicting acute acetaminophen hepatotoxicity with acetaminophen-aminotransferase multiplication product and the Psi parameter. Clin Toxicol (Phila). 2014;52(5):506–511.
[28] Wong A, Sivilotti MLA, Gunja N, et al. Accuracy of the paracetamol-aminotransferase product to predict hepatotoxicity in paracetamol overdose treated with a 2-bag acetylcysteine regimen. Clin Toxicol (Phila). 2018;56(3):182–188.
[29] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
[30] Egan H, Isbister GK, Robinson J, et al. Retrospective evaluation of repeated supratherapeutic ingestion (RSTI) of paracetamol. Clin Toxicol (Phila). 2019;57(8):703–711.
[31] Nacca NE, Hodgman M. APAP × at in staggered, chronic and time unknown acetaminophen overdoses. Clinical Toxicology. 2015;53(4):391.
[32] Offerman S, Young M. Use of the initial acetaminophen concentration times serum aminotransferase product to predict significant liver enzyme elevations after acetaminophen overdose. Clin Toxicol. 2011;49(6):591.
[33] Doebler P, Holling H. Meta-analysis of diagnostic accuracy with mada. R Packag. 2015;1:15.
[34] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–1558.
[35] Steinhauser S, Schumacher M, Rücker G. Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. BMC Med Res Methodol. 2016;16(1):97. 2016/08/12
[36] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–536.
[37] Daly FF, Fountain JS, Murray L, et al. Guidelines for the management of paracetamol poisoning in Australia and New Zealand–explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust. 2008;188(5):296–301.
[38] Dargan PI, Jones AL. Management of paracetamol poisoning. Trends Pharmacol Sci. 2003;24(4):154–157.
[39] Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-Acetylcysteine in the treatment of acetaminophen overdose. N Engl J Med. 1988;319(24):1557–1562. 1988/12/15
[40] Leventhal TM, Gottfried M, Olson JC, et al. Acetaminophen is undetectable in plasma from more than half of patients believed to have acute liver failure due to overdose. Clin Gastroenterol Hepatol. 2019;17(10):2110–2116.
[41] Huang HS, Ho CH, Weng SF, et al. Long-term mortality of acetaminophen poisoning: a nationwide population-based cohort study with 10-year follow-up in Taiwan. Scand J Trauma Resusc Emerg Med. 2018;26(1):5.
[42] O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439–445.
[43] Mitchell SJ, Kane AE, Hilmer SN. Age-related changes in the hepatic pharmacology and toxicology of paracetamol. Curr Gerontol Geriatr Res. 2011;2011:624156–624156.