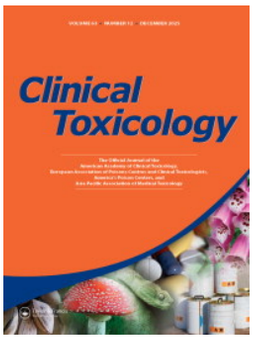

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# Diagnostic utility of the paracetamol concentration aminotransferase activity multiplication product in identifying patients exceeding the 150 mg/L treatment line on the Rumack–Matthew nomogram

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**ABSTRACT**

**Background:** Paracetamol poisoning and the associated liver damage can be effectively managed by the timely administration of acetylcysteine. Most treatment protocols depend on the line intersecting 150 mg/L (992 µmol/L) at 4 h on the Rumack–Matthew nomogram (150-treatment line), which requires accurate determination of ingestion time to assess risk. The paracetamol concentration aminotransferase activity multiplication product has emerged as a predictive measure for paracetamol-induced hepatotoxicity in patients receiving acetylcysteine, without necessitating the precise knowledge of ingestion time. This study aims to assess the diagnostic performance of the multiplication product in identifying cases with paracetamol concentrations surpassing the 150-treatment line and to establish an optimal cutoff value for this clinical tool.

**Methods:** A retrospective review of acute paracetamol overdoses admitted to Siriraj Hospital in Bangkok, Thailand, from January 2007 to December 2016 was conducted. The multiplication product was calculated by multiplying the serum paracetamol concentration (mg/L) by the higher activity of alanine aminotransferase or aspartate aminotransferase (U/L), both measured from simultaneous blood samples. The diagnostic accuracy of the multiplication product in predicting paracetamol concentrations above the 150-treatment line was evaluated through receiver operating characteristic curve analysis, sensitivity, and specificity. The optimal cutoff value was determined using the Youden index.

**Results:** Among the 934 patients included, 43.5% (406 cases) presented paracetamol concentrations above the 150-treatment line. The multiplication product had an area under the receiver operating characteristic curve of 0.874. An optimal cutoff of 1,501.6 mg*U/L$^2$ yielded a sensitivity of 84.8% and a specificity of 79.8%.

**Discussion:** The 150-treatment line on the Rumack–Matthew nomogram demonstrated a sensitivity of 100.0% (95% CI: 93.7 – 100.0%) and a specificity of 60.2% (95% CI: 56.9 – 63.5%) for predicting hepatotoxicity. In comparison, the 1,500 mg*U/L$^2$ cutoff of the paracetamol concentration aminotransferase activity multiplication product showed a sensitivity of 98.3% (95% CI: 90.6 – 100.0%) and a specificity of 50.7% (95% CI: 47.4 – 54.1%).

**Conclusions:** The paracetamol concentration aminotransferase activity multiplication product demonstrates predictive ability for serum paracetamol concentrations at or above the 150-treatment line on the Rumack–Matthew nomogram.

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Acetylcysteine; aminotransferase; paracetamol overdose; Rumack–Matthew nomogram; time-unknown ingestion

## Introduction

Paracetamol overdose is among the leading causes of drug-induced hepatotoxicity globally [1]. Timely administration of acetylcysteine is highly effective for preventing and managing hepatotoxicity in patients with paracetamol overdose [2]. For over 40 years, the Rumack–Matthew nomogram, which involves plotting the measured serum paracetamol concentration against a finite amount of time since ingestion, has been the requisite in predicting hepatotoxicity and the subsequent initiation of treatment with acetylcysteine [3]. When started within 8 h of ingestion, acetylcysteine significantly reduces the risk of hepatotoxicity, whereas its delayed administration can increase the risk to as high as 44% [2,4]. Consequently, ambiguities

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in determining the time since ingestion can pose limits to the applicability of the nomogram [2].

In 2010, Sivilotti and colleagues [5] conducted a retrospective study to assess whether the multiplication product of paracetamol concentration and concurrent aminotransferase activities could serve as a predictive tool for hepatotoxicity risk in patients receiving acetylcysteine treatment following acute paracetamol overdose. The multiplication product demonstrated high specificity at an upper cutoff of 10,000 mg*U/L$^2$, above which the risk of hepatotoxicity was increased, as well as high sensitivity at a lower cutoff of 1,500 mg*U/L$^2$ [6–9]. This means that patients with multiplication products exceeding this threshold are at higher risk of developing hepatotoxicity compared to those whose values are below the cutoff. This carried the implication that this value can be used clinically to indicate the need for antidote treatment.

Another notable advantage of the multiplication product method for predicting hepatotoxicity was that it did not require the exact time of ingestion to be known. The only discrete numerical inputs required were the paracetamol concentration and aminotransferase activity, both obtained from simultaneously collected blood samples [5]. This method diverges from the current recommendations, which advise that when the time of ingestion is unknown, acetylcysteine therapy should be initiated if the serum paracetamol concentration is detectable or aminotransferase activity is elevated [10]. The overtreatment invariably associated with this default approach is generally regarded as a worthwhile trade-off, given the possible hepatotoxicity that could ensue if untreated.

Even though both of these surrogate methods for determining the need for antidote treatment have been employed in clinical practice, neither has been validated against the Rumack–Matthew nomogram, the established reference standard. Such validation can offer added affirmation for practitioners in choosing the appropriate risk classification tool and provide some degree of certainty where so many unknowns already exist. Leveraging the advantage of having clinical toxicology and clinical chemistry laboratories at our institution, we conducted this study to address such potential knowledge gaps.

### Objectives

The primary objective of this study is to evaluate the accuracy of the paracetamol concentration aminotransferase activity multiplication product in predicting serum paracetamol concentrations surpassing the line crossing the 150 mg/L (992 µmol/L) concentration at the 4 h mark on the Rumack-Matthew nomogram (the 150-treatment line). The outcomes include identifying the optimal cutoff point for the multiplication product in this predictive capacity and assessing its diagnostic accuracy at a cutoff value of 1,500 mg*U/L$^2$ for predicting paracetamol concentrations above the 150-treatment line. Additionally, the study aims to compare the performance of the multiplication product with the default approach recommended when the time of ingestion is unknown.

## Methods

We conducted a retrospective analysis of medical records from patients admitted to Siriraj Hospital in Bangkok, Thailand, spanning the period from January 1, 2007, to December 31, 2016, with the diagnosis of paracetamol overdose. Exclusion criteria were patients aged less than 12 years, cases involving ingestion of modified-release paracetamol tablets, mixed overdose incidents, staggered overdoses (ingestion over a period longer than 1 h), initial paracetamol concentration measurement taken before 4 h or after 24 h post-ingestion and those lacking available information about the time of overdose. The data extracted from these medical records consisted of demographic information, dosage details, timing and method of ingestion, initial and follow-up results of paracetamol, aminotransferase, and pertinent clinical chemistry assessments. The research protocol received approval from the Human Research Protection Unit at the Faculty of Medicine Siriraj Hospital, Mahidol University (protocol number 436/2564). This study adhered to the principles outlined in the Declaration of Helsinki.

### Calculation of the 4 h paracetamol concentration

The 4 h paracetamol concentration was calculated using a back-extrapolation method based on the formula $C4 = Ct/2e^{-(0.693/4)t}$, in which Ct represents the recorded paracetamol concentrations, and 't' denotes the time lapse in hours between ingestion and blood collection [11]. This extrapolation method facilitated comparisons across different patient groups. The calculation used the half-life of 4 h to mirror the gradient observed on the Rumack-Matthew nomogram.

### The paracetamol concentration aminotransferase activity multiplication product

The paracetamol concentration aminotransferase activity multiplication product value was determined by multiplying the paracetamol concentration (in mg/L) with either

the aspartate aminotransferase or alanine aminotransferase (in unit/L) activity, whichever was higher.

### *Classification of hepatotoxicity risk based on different risk assessment methods*

All patients were classified as either at risk (positive) or not at risk (negative) for hepatotoxicity using three separate assessment methods: the Rumack–Matthew nomogram (considered the gold standard), the multiplication product, and the default method. For the Rumack–Matthew nomogram, each patient's serum paracetamol concentration was plotted against the time since ingestion. Cases were labelled as "treatment line positive" if the value was at or above the treatment threshold, and "treatment line negative" if it fell below. For the multiplication product, each case was assessed using a predefined cutoff value of 1,500 mg*U/L$^2$. Cases were classified as "multiplication product positive" if the value was equal to or greater than the cutoff, and "negative" if below. For the default classification, patients were considered "default method positive" if either the serum paracetamol concentration exceeded 10 mg/L (66.2 µmol/L) or the aminotransferase activity was greater than 50 U/L. They were classified as "default method negative" if paracetamol was undetectable and aminotransferase activity was 50 U/L or lower. Only the first available set of laboratory data for each patient was used for the analysis. The outcome of hepatotoxicity was defined by aminotransferase activities of at least 1,000 U/L during follow-up. The subjects were analyzed both as a whole and in subgroups based on blood test times: 4 h to 8 h, 8 h to 12 h, 12 h to 16 h, and 16 h or later.

During the study period, the clinical management of acute paracetamol overdose at Siriraj Hospital included gastrointestinal decontamination and a 21 h intravenous acetylcysteine regimen administered using the three-bag method: 150 mg/kg over 30–60 min, followed by 50 mg/kg over 4 h, and then 100 mg/kg over 16 h, for a total dose of 300 mg/kg. Activated charcoal was typically administered to patients presenting within four hours of ingestion. Oral acetylcysteine was used only when intravenous administration was not tolerated or contraindicated. At presentation, serum paracetamol concentration and aminotransferase activity were measured from the same blood sample.

### *Statistical analyses*

Descriptive statistics were reported as frequency (percentage) or mean with 95% confidence interval (CI); medians with interquartile range (IQR) were used for non-normally distributed data. Group differences were tested with Student's t-test or Mann–Whitney U-test, and categorical variables with chi-squared or Fisher's exact test. Diagnostic accuracy was evaluated using receiver operating characteristic curves and the area under the curve (AUC). Optimal cutoffs were determined by the Youden index, and sensitivity and specificity (95% CI) were calculated. A $P$ value <0.05 was considered significant. Analyses were performed using MedCalc 19.6.4, and figures with PASW Statistics 30.

## Results

During the study period, 1,286 patients presented to Siriraj Hospital with paracetamol overdose. After excluding 352 patients, 934 patients were included in the analysis (Figure 1). The subjects consisted of 766 females (82.0%) with a median age of 23 years (IQR: 20–28 years). Among these, 406 subjects (43.5%) had paracetamol concentrations at or above the 150-treatment line. Compared to those below this threshold, individuals in the treatment line positive group had significantly higher initial paracetamol concentrations, aspartate aminotransferase activities, and multiplication product (Table 1 and Figure 2). Hepatotoxicity occurred in 57 patients (6.1%), 189 patients (20.1%) had peak aminotransferase activities of 50–999 U/L, and no patient mortality occurred in our series.

Table 2 presents the receiver operating characteristic curve analysis of the paracetamol concentration aminotransferase activity multiplication product for predicting paracetamol concentrations above the 150-treatment line (Figures 3(A–E)). Overall, the AUC is 0.874, with an optimal cutoff at 1,501.6 mg U/L$^2$, yielding a sensitivity of 84.9% and a specificity of 79.6%. In the subgroup with blood test times between 4 h and 8 h after ingestion, the cutoff remains 1,501.6 mg*U/L$^2$, with a sensitivity of 94.8% and a specificity of 76.9%. In the 8 h to 12 h group, the optimal cutoff decreases to 1,267.2 mg*U/L$^2$, with a sensitivity of 76.4% and a specificity of 100.0%. In the 12 h to 16 h group, the cutoff further decreases to 575 mg*U/L$^2$, with a sensitivity of 85.1% and a specificity of 93.3%. Finally, the optimal cutoff decreases to 414 mg*U/L$^2$ in the group with blood tests taken at 16 h or later.

Table 3 presents the receiver operating characteristic curve analysis of the paracetamol concentration aminotransferase activity multiplication product at a cutoff of 1,500 mg*U/L$^2$, alongside the default method for predicting paracetamol concentrations above the 150-treatment line, with a comparison of the AUC. For all subjects, as well as in the subgroups tested between

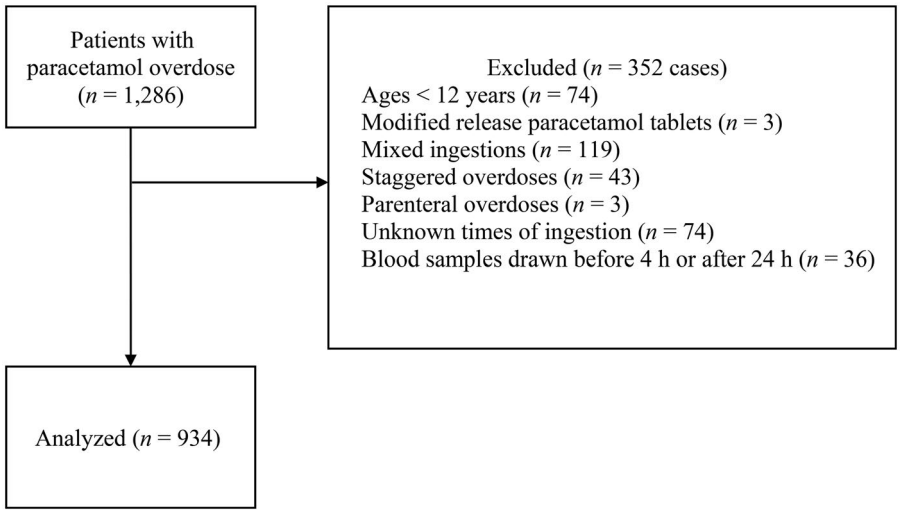



**Figure 1.** Patient flow diagram.

**Table 1.** Clinical characteristics of all cases, comparing groups with and without paracetamol concentrations at or above the 150-treatment line on the Rumack–Matthew nomogram.

| Characteristics | All cases (*n* = 934) | Above 150-treatment line (*n* = 406) | Below 150-treatment line (*n* = 528) |
|---|---|---|---|
| Age (years), median (IQR) | 23 (20–28) | 23 (20–27) | 23 (20–28) |
| Female, *n* (%) | 766 (82.0) | 335 (82.5) | 432 (81.8) |
| Initial paracetamol concentration (mg/L), median (IQR) | 100.3 (57.6–157.8) | 162.0 (114.5–205.9) | 68.0 (40.3–103.5) |
| Initial paracetamol concentration, μmol/L, median (IQR)) | 668.7 (384.0–1,052.0) | 1,080.0 (763.3–1,372.7) | 453.3 (268.7–690.0) |
| Extrapolated paracetamol concentration at 4 h (mg/L), median (IQR) | 137.4 (85.2–229.7) | 251.5 (191.5–379.6) | 94.4 (61.0–122.9) |
| Extrapolated paracetamol concentration at 4 h (μmol/L), median (IQR) | 916.0 (568.0–1,531.3) | 1,676.7 (1,276.7–2,530.7) | 629.3 (406.7–819.3) |
| Initial aspartate aminotransferase activity (U/L), median (IQR) | 15 (13–20) | 15 (12–22) | 15 (13–19) |
| Initial alanine aminotransferase activity (U/L), median (IQR) | 13 (10–18) | 13 (9–20) | 11 (14–18) |
| Paracetamol concentration aminotransferase activity multiplication product (mg * U/L$^2$), median (IQR) | 1,656,6 (984.8–2,677.2) | 2,660.0 (1,868.0–3,762.7) | 1,183.0 (679.0–1,694.9) |

4 h and 8 h and 8 h and 12 h post-ingestion, the multiplication product showed significantly larger AUC compared to the default method (Figures 4(A-C)). In these settings, the sensitivities and specificities of the multiplication product were acceptable, whereas the default method provided very high sensitivity but very low specificity. In the subgroup tested between 12 h and 16 h post-ingestion, there was no significant difference in AUC between the multiplication product and the default method (Figure 4(D)). The multiplication product achieved 100% specificity, while the default method yielded 100% sensitivity. Finally, in the subgroup tested at 16 h or later, the AUC of the default method was larger than that of the multiplication product, though the difference was not statistically significant (Figure 4(E)). Both methods achieved 100% specificity, but the sensitivity of the default method (84.2%) was higher than that of the multiplication product (72.2%).

The 150-treatment line on the Rumack–Matthew nomogram demonstrated a sensitivity of 100.0% (95% CI: 93.7–100.0%) and a specificity of 60.2% (95% CI: 56.9–63.5%) for predicting hepatotoxicity. In comparison, the 1,500 mg * U/L$^2$ cutoff of the paracetamol concentration aminotransferase activity multiplication product showed a sensitivity of 98.3% (95% CI: 90.6–100.0%) and a specificity of 50.7% (95% CI: 47.4–54.1%).

One notable case in (Figure 2(B)). was an 18-year-old female who ingested 15 g of paracetamol (365.9 mg/kg). Fourteen hours post-ingestion, her multiplication product was 1,315.2 mg * U/L$^2$, derived from a serum paracetamol concentration of 109.6 mg/L and alanine aminotransferase activity of 12 U/L. Her peak alanine aminotransferase activity, measured at 57 h post-ingestion, was 1,648 U/L. She received intravenous acetylcysteine until 81 h post-ingestion and recovered uneventfully.

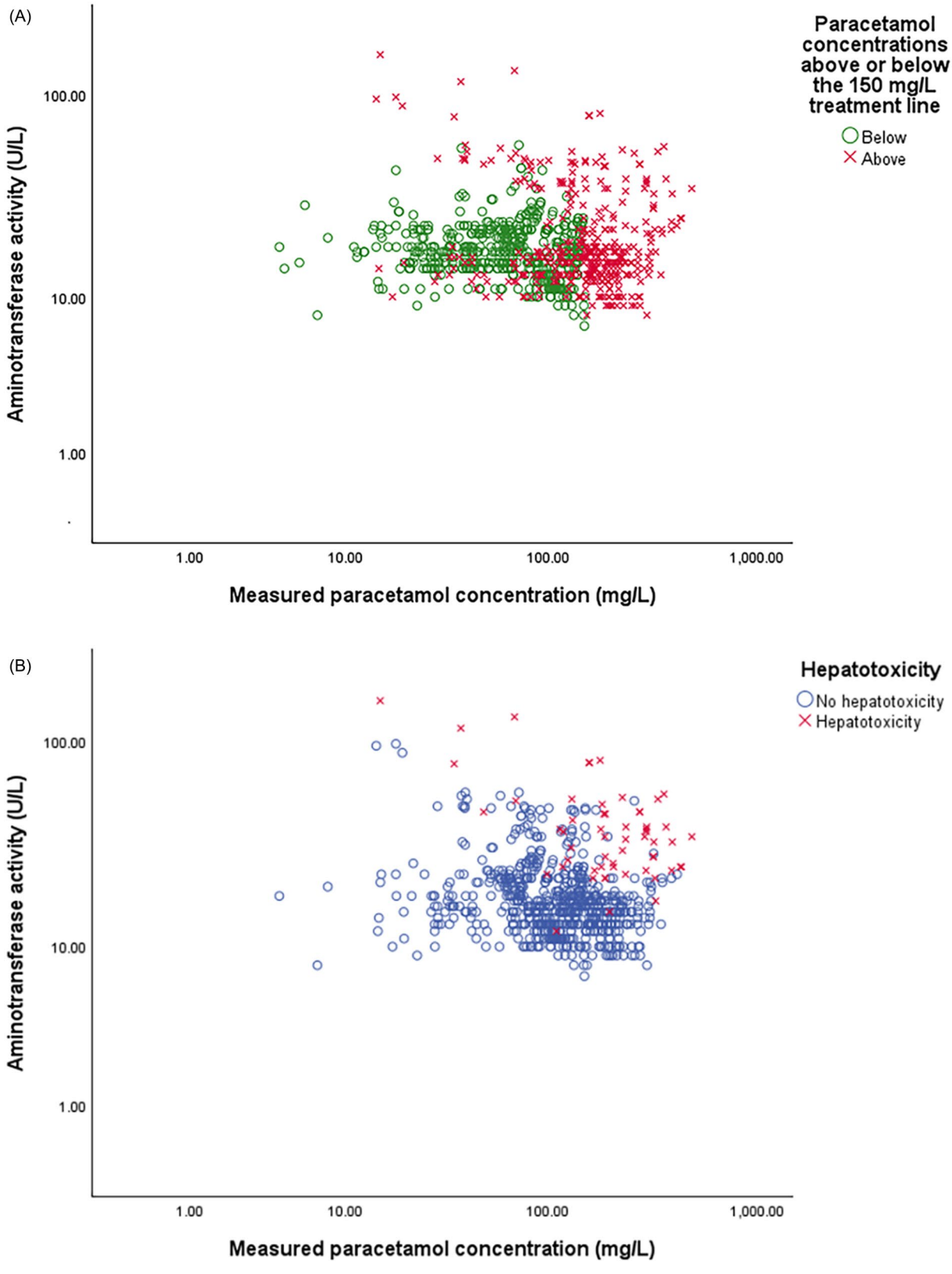



**Figure 2.** Scatter plots on log-log scales showing the relationship between measured paracetamol concentrations at presentation and aminotransferase activities. The diagonal line represents a paracetamol concentration aminotransferase activity multiplication product of 1,500 mg*U/L$^2$. A: Data are categorized based on whether paracetamol concentrations at presentation fall above or below the 150-treatment line on the Rumack–Matthew nomogram. B: Data are categorized based on the presence or absence of hepatotoxicity.

**Table 2.** Receiver operating characteristic curve analysis of the paracetamol concentration aminotransferase activity multiplication product for predicting serum paracetamol concentrations above the 150-treatment line on the Rumack–Matthew nomogram, stratified by time since ingestion.

| Subjects | Area under the curve (95% CI) | Optimal cutoff (mg*U/L$^2$) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|---|---|---|---|---|
| All cases ($n$ = 934) | 0.874 (0.851–0.894) | 1,501.6 | 84.9 (81.1–88.3%) | 79.6 (75.9–82.9%) |
| Time 4-8 h ($n$ = 673) | 0.913 (0.890–0.932) | 1,501.6 | 94.8 (91.5–97.1%) | 76.9 (72.8–80.7%) |
| Time 8-12 h ($n$ = 154) | 0.937 (0.886–0.969) | 1,267.2 | 76.4 (67.3–83.9%) | 100.0 (91.9–100.0%) |
| Time 12-16 h ($n$ = 77) | 0.950 (0.875–0.987) | 575 | 85.1 (71.7–93.8%) | 93.3 (77.9–99.0%) |
| Time ≥16 h ($n$ = 26) | 0.972 (0.819–0.992) | 414 | 83.3 (58.6–96.2%) | 100.0 (62.9–100.0%) |

The table presents the optimal cutoff values, determined using the Youden index, along with the corresponding sensitivity and specificity at each time interval.

**Table 3.** Areas under the receiver operating characteristic curves, along with sensitivity and specificity, for predicting whether paracetamol concentrations are above the 150-treatment line on the Rumack–Matthew nomogram at various blood test intervals.

| | Paracetamol concentration aminotransferase activity multiplication product ≥1,500 mg*U/L$^2$ | | | Detectable paracetamol concentration or elevated aminotransferase activity (default method) | | | |
|---|---|---|---|---|---|---|---|
| Subjects | Area under the curve (95% CI) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Area under the curve (95% CI) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | $P$ value |
| All cases | 0.787 (0.760–0.813) | 84.9 (81.1–88.3%) | 79.6 (75.9–82.9%) | 0.527 (0.494–0.559) | 99.3 (97.9–99.9%) | 6.1 (4.2–8.5%) | <0.001 |
| Time 4–8 h | 0.882 (0.791–0.849) | 94.8 (91.5–97.1%) | 76.9 (72.8–80.7%) | 0.514 (0.476–0.552) | 100.0 (98.5–100.0%) | 2.9 (1.6–4.9%) | <0.001 |
| Time 8–12 h | 0.853 (0.782–0.909) | 70.9 (61.5–79.2%) | 100.0 (92.0–100.0%) | 0.514 (0.426–0.601) | 100.0 (96.3–100.0%) | 2.8 (0.1–14.5%) | <0.001 |
| Time 12–16 h | 0.790 (0.684–0.873) | 57.5 (42.2–71.7%) | 100.0 (88.4–100.0%) | 0.667 (0.552–0.768) | 100.0 (92.9–100.0%) | 33.3 (17.3–52.8%) | 0.116 |
| Time ≥16 h | 0.868 (0.683–0.966) | 72.2 (46.5–90.3%) | 100.0 (63.1–100.0%) | 0.921 (0.750–0.987) | 84.2 (60.4–96.6%) | 100.0 (63.1–100.0%) | 0.475 |

Two methods are compared: (1) the paracetamol concentration aminotransferase activity multiplication product (cutoff: 1,500 mg*U/L$^2$), and (2) the "detectable paracetamol concentration or elevated aminotransferase activity" method (default method). $P$ values are provided for comparisons of the areas under the curves between the two methods.

## Discussion

For clinicians, the primary goal in the management of paracetamol overdose is to assess the risk of hepatotoxicity to facilitate the treatment decisions that will most ensure patient safety while cost-effectiveness is maintained. Currently, the Rumack–Matthew nomogram, the first clinical tool developed for assessing the risk of hepatotoxicity in acute paracetamol overdose, remains the standard of care for initiating acetylcysteine therapy [2,3]. The aim of this study is to evaluate the accuracy of the paracetamol concentration aminotransferase activity multiplication product in predicting paracetamol concentrations above the 150-treatment line on the Rumack–Matthew nomogram in the hopes that it might be used as a surrogate tool when the time of ingestion is not available.

In general, our study demonstrates that the areas under the receiver operating characteristic curves for the multiplication product ranged from good to very good (0.874 to 0.972). And despite the optimal cutoff values decreasing over time, from 1,501.6 mg*U/L$^2$ at 4–8 h post-ingestion to 414.0 mg*U/L$^2$ beyond 16 h post-ingestion, high sensitivity (76.4% to 94.8%) and specificity (76.9% to 100%) are maintained across all time interval subgroups (Table 2).

When the cutoff of 1,500 mg*U/L$^2$ is applied, the multiplication product demonstrates high sensitivity in the 4 h to 8 h post-ingestion window. However, beyond 8 h, sensitivity decreases while specificity increases. This contrasts with the default method, which maintains high sensitivity across all time periods but exhibits low specificity prior to 16 h post-ingestion. Notably, at 16 h and beyond, the specificity of the default method reaches 100%, with a sensitivity that surpasses that of the multiplication product. Concurrently, the areas under the receiver operating characteristic curves for the multiplication product with the 1,500 mg*U/L$^2$ cutoff are higher than those of the default method between 4 h and 16 h post-ingestion. Beyond 16 h, the AUC for the default method exceeds that of the multiplication product, primarily due to improved specificity.

The principle behind the multiplication product method is rooted in the established relationship between a high serum paracetamol concentration and concurrently elevated aminotransferase activity seen in patients who have developed hepatotoxicity [5–8]. The increased aminotransferase activity is believed to result from an earlier and more rapid rise in aminotransferase activities in cases of paracetamol toxicity [12,13]. In a study by Al-Hourani and colleagues [12] involving

410 patients with acute paracetamol overdose, patients whose aminotransferase activity exceeded the upper normal limit (50 U/L) within 0–8 h post-ingestion showed a sensitivity of 100% (95% CI: 44–100%) and a specificity of 87% (95% CI: 82–90%) for predicting hepatotoxicity. During the 8 h to 24 h testing period, sensitivity decreased to 50% (95% CI: 0–100%), while specificity remained relatively high at 84% (95% CI: 73–92%) [12]. This study emphasizes that aminotransferases can begin to rise within 8 h post-ingestion, offering valuable diagnostic insights for predicting hepatotoxicity.

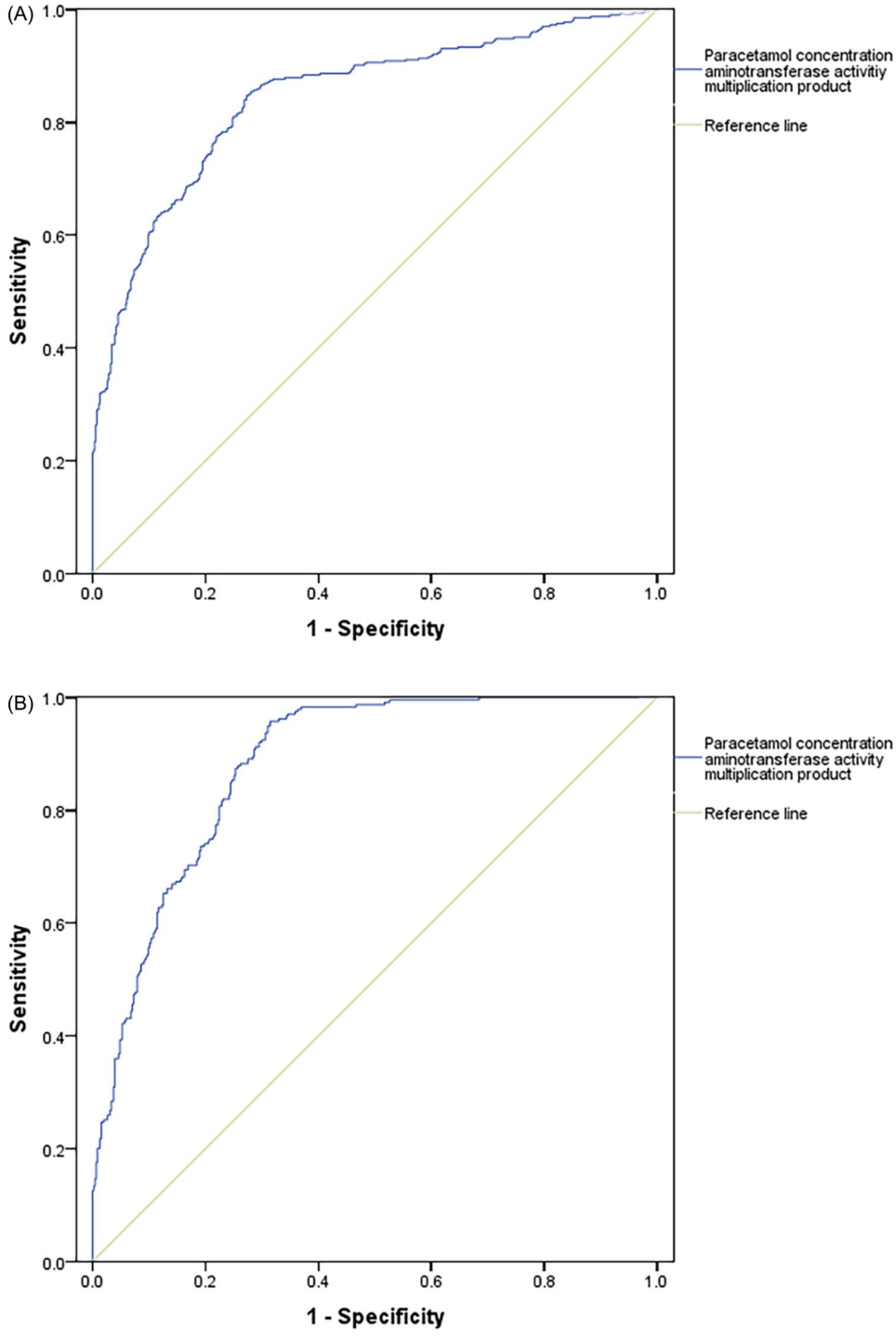



**Figure 3.** Receiver operating characteristic curves for predicting whether paracetamol concentrations are above or below the 150-treatment line on the Rumack–Matthew nomogram, using the paracetamol concentration aminotransferase activity multiplication product at various blood test intervals. A: All patients. B: Blood test timing: 4–7.58 h post-ingestion. C: Blood test timing: 8–11.59 h post-ingestion. D: Blood test timing: 12–15.59 h post-ingestion. E: Blood test timing: 16 h or more post-ingestion.

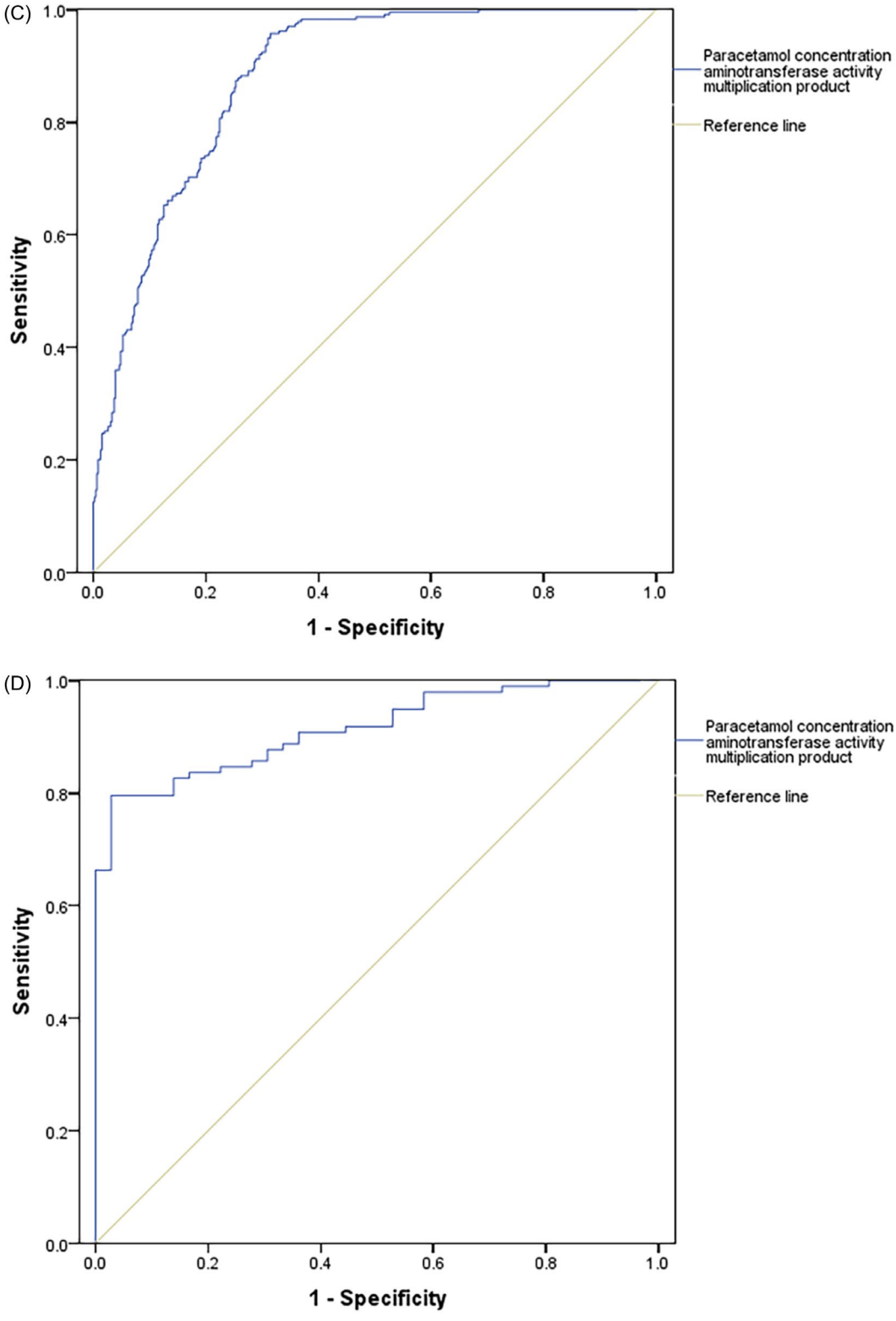



Figure 3. Continued.

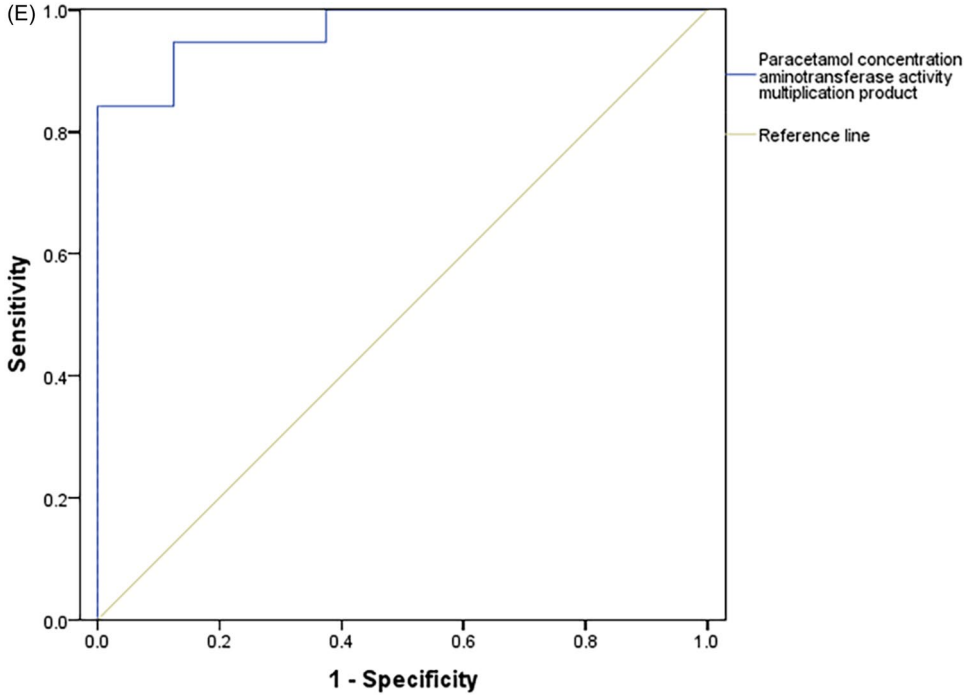



**Figure 3.** Continued.

These findings in the literature, coupled with data from this research, prompt careful considerations of how the multiplication product can be applied in clinical practice. Identifying the cutoff value that offers the optimal balance between sensitivity and specificity is crucial, especially in cases where the exact time of ingestion is unknown, which is where the strength of the multiplication product lies. In such cases, applying the multiplication product cutoff of 1,500 mg*U/L$^2$ appears to be a logical choice, as it closely approximates the optimal cutoff of 1,501.6 mg*U/L$^2$ determined by the Youden Index. It is also a prudent choice, as the 1,500 mg*U/L$^2$ cutoff demonstrates very high sensitivity (approaching 100%) for excluding hepatotoxicity. In the original work reported by Sivilotti and colleagues [5] in 2010, no patients with a product below this threshold developed liver injury, regardless of the timing of acetylcysteine administration.

Interestingly, the optimal cutoff of the multiplication product decreases with increasing time after ingestion, while specificity rises. This reflects a "circular" effect in which both the predictor and the outcome threshold are tied to time. The 150-treatment line declines over time, so at later times, patients above the line have lower paracetamol concentrations than earlier cases. Since the multiplication product includes paracetamol concentration, its values also fall over time, leading to lower optimal cutoffs. By the later time points, treatment line positive patients usually have both persistent paracetamol concentrations and increased aminotransferase activities, while treatment line negative cases have low values for both, widening the gap between groups and improving specificity.

The outlier case in Figure 2(B) illustrates that low aminotransferase activity early after ingestion can yield a low multiplication product despite clinically significant paracetamol ingestion, underscoring that the multiplication product should not be used in isolation to guide acetylcysteine initiation. Should the multiplication product be used, the limitation of its lower sensitivity, must be addressed. In this regard, routine follow-up of aminotransferase activity at 24 h post-ingestion can be implemented, with acetylcysteine initiated in patients showing elevated enzyme activities. Alternatively, a more conservative approach using the default method remains a viable option. However, its limited specificity in identifying paracetamol concentrations exceeding the 150-treatment line, particularly in patients presenting within 16 h of ingestion, warrants consideration. Lower specificity increases the likelihood of unnecessary acetylcysteine administration, thereby exposing patients to potential adverse effects. This is particularly concerning as acetylcysteine's adverse effects, such as anaphylactoid reactions, can be life-threatening and are reported to occur more frequently in patients with lower serum paracetamol concentrations [14,15]. Moreover, the financial burden to patients and the healthcare system that is the direct consequence of overtreatment cannot be underestimated. Finally, we emphasize that this study does not

seek to replace the Rumack–Matthew nomogram, but to examine how the multiplication product may support decisions on initiating acetylcysteine in acute paracetamol overdose.

Our study has certain limitations, primarily due to its retrospective design. Data were collected through a review of clinical service records, and the reported time of ingestion may be inaccurate, potentially leading to

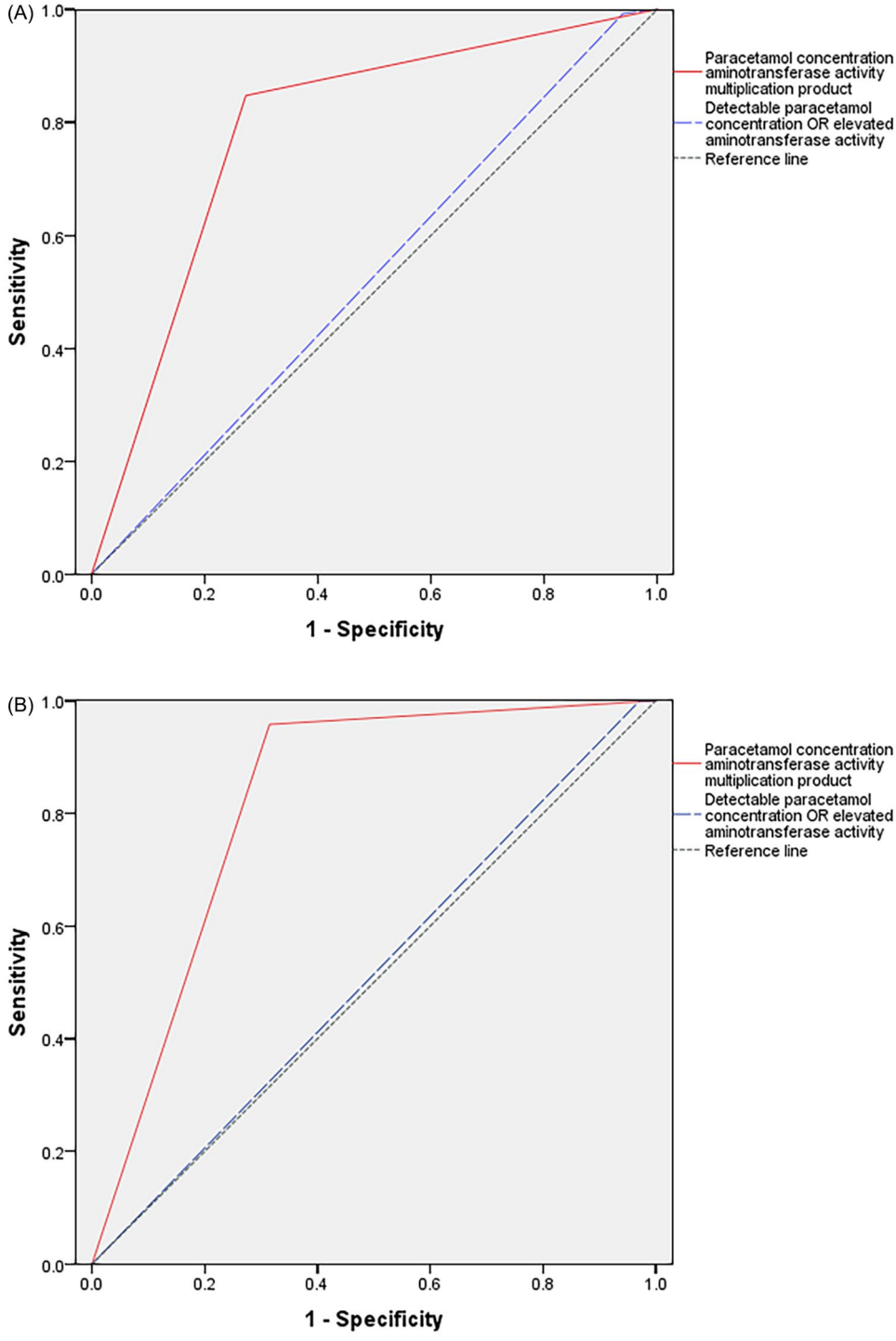
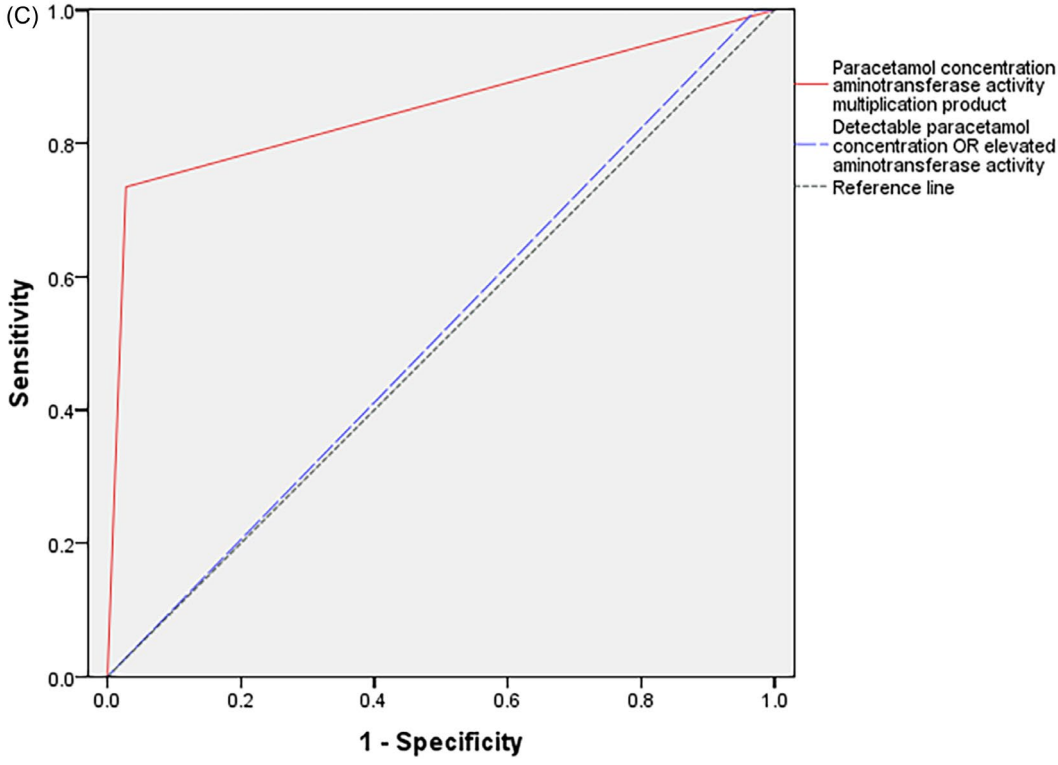



**Figure 4.** Receiver operating characteristic curves for predicting whether paracetamol concentrations are above or below the 150-treatment line on the Rumack–Matthew nomogram at various blood test intervals, using two methods: (1) the paracetamol concentration aminotransferase activity multiplication product (cutoff: 1,500 mg * U/L$^2$), and (2) the "detectable paracetamol concentration OR increased aminotransferase activity" method (Default Method). A: All patients. B: Blood test timing: 4–7.59 h post-ingestion. C: Blood test timing: 8–11.59 h post-ingestion. D: Blood test timing: 12–15.59 h post-ingestion. E: Blood test timing: 16 h or more post-ingestion.



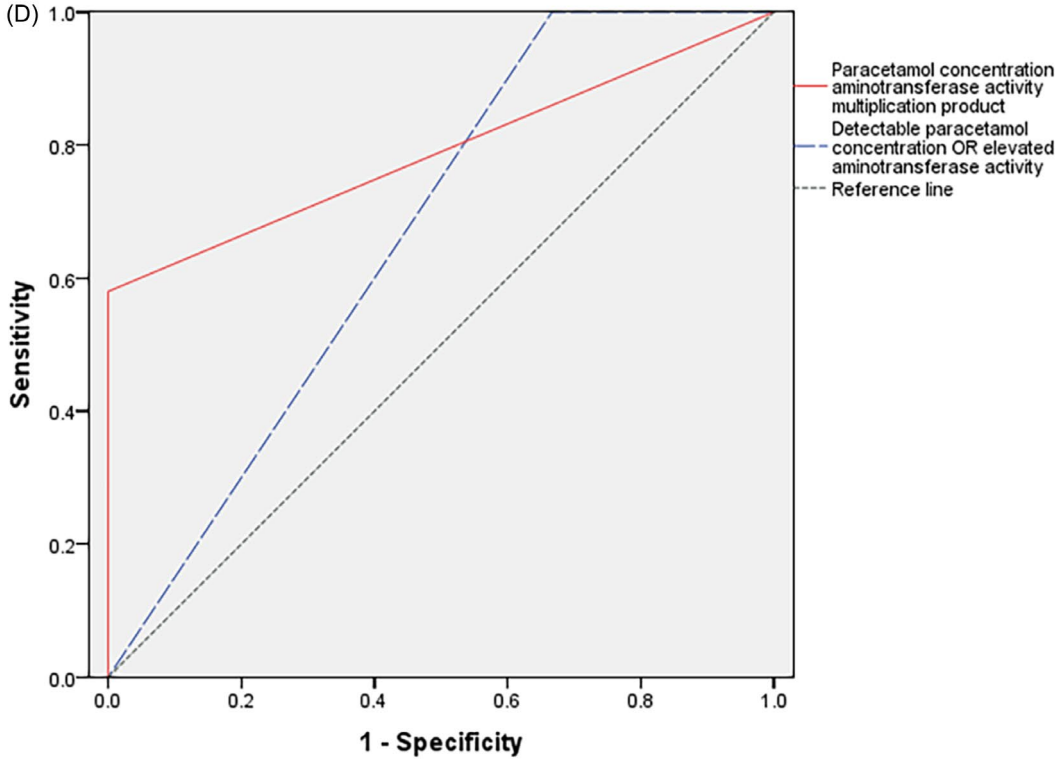




**Figure 4.** Continued.

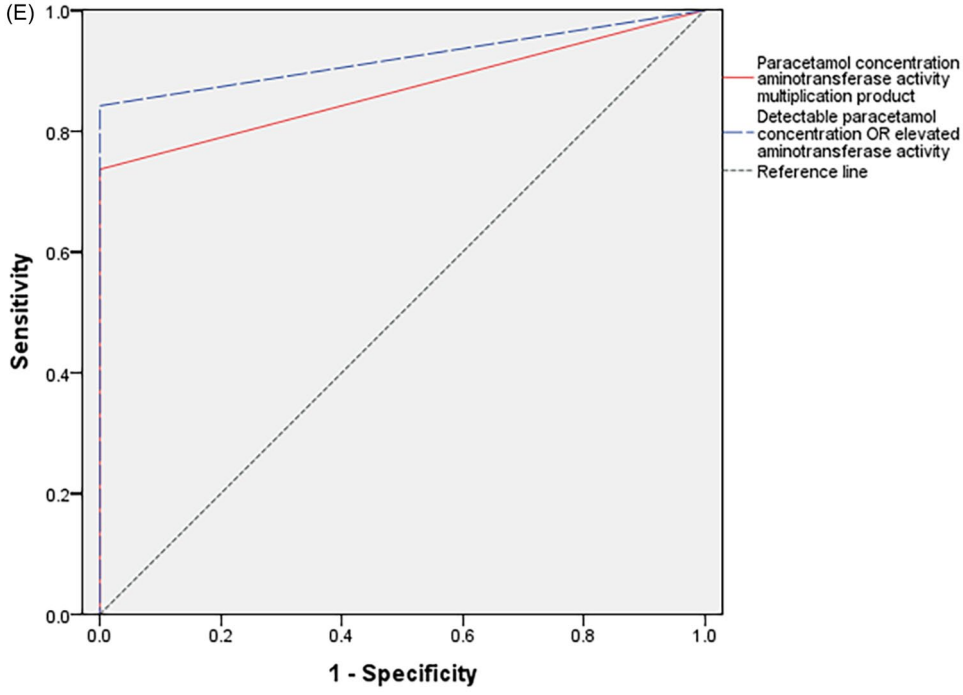



Figure 4. Continued.

misclassification of patients as being above or below the 150-treatment line on the Rumack–Matthew nomogram. In addition, we have assumed a paracetamol elimination half-life of 4 h, which may not be correct in all patients, and thus our back calculations may be incorrect too. We recommend that future research whose aims are to achieve these objectives be conducted prospectively, with proactive verification of the time of paracetamol ingestion to improve accuracy.

## Conclusion

The multiplication product of 1,500 mg*U/L$^2$ is shown to be an accurate predictor of serum paracetamol concentration at or above the 150-treatment line on the Rumack–Matthew nomogram.

## Authors' contributions

The study was designed, and data were collected and analyzed by SC, PM, JP, and CC. SC and CC wrote the initial draft of the manuscript, with contributions from PM and JP. All authors have reviewed and agreed on the content of the final manuscript.

## Disclosure statement

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## Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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