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Plasma procalcitonin may be an early predictor of liver injury in acetaminophen poisoning: A prospective cohort study

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Abstract

Background and Aims: Acetaminophen is a common cause of poisoning and liver injury worldwide; however, patient stratification is suboptimal. We aimed to assess the contribution of admission plasma procalcitonin concentration (PCT) to better identify acetaminophen-poisoned patients likely to develop liver injury.

Methods: We conducted a prospective observational cohort study including all acetaminophen-poisoned patients requiring N-acetylcysteine admitted in a toxicological intensive care unit between 2012 and 2017. Multivariate analysis was performed using a Cox regression model to investigate factors associated with liver injury, defined as an increase in alanine aminotransferase (ALT) >100 IU/L.

Results: One hundred seventeen patients (age, 32 years (21–53), median [25th–75th percentiles]) were included after self-ingesting 16 g (9–30) acetaminophen and received N-acetylcysteine infusion administered within a median 6 h-delay (4–12) from exposure. Co-ingestions were reported in 77% of patients. Rumack–Matthew nomogram was non-interpretable in 47% cases. Liver injury occurred in 38 patients (32%) with a median peak ALT of 2020 IU/L (577–4248). In liver injury patients, admission PCT was significantly increased in comparison to patients without liver injury (21.5 ng/ml (3.2–44.9) versus 0.1 ng/ml (0–0.4), respectively, $p < 0.01$). The increase in PCT preceded the increase in ALT by 33 h (10–74). In a multivariate analysis, PCT > 1 ng/ml was significantly associated with liver injury (hazard ratio, 7.2 [95% confidence interval, 2.3–22.6; $p < 0.001$]). PCT (area under the receiver-operating characteristics curve, 0.91 [95%CI: 0.84–0.97]) predicted liver injury with sensitivity, specificity, negative, and positive predictive values of 0.92, 0.84, 0.96, and 0.73, respectively.

Conclusion: PCT on admission is associated with liver injury in acetaminophen poisoning. PCT might be used as a predictive tool of liver injury to improve clinical decision-making.

KEYWORDS
acetaminophen, acute liver injury, biomarker, drug-induced liver injury, hepatotoxicity, paracetamol, PCT, poisoning, predictive tool, procalcitonin

INTRODUCTION

Acetaminophen, one of the most commonly prescribed drugs worldwide, is the leading cause of acute poisoning and liver injury (LI) in the developed countries.[1–3] For more than 4 decades, a nomogram has been used to predict acetaminophen-induced hepatotoxicity, helping physicians deciding whether to treat the poisoned patient with N-acetylcysteine (NAC) or not.[4] Nevertheless, evaluating the risk of LI using the nomogram has not been validated in several common scenarios, including (1) chronic overdose, (2) co-ingested drugs slowing gastrointestinal absorption, (3) unknown time from ingestion to presentation, and (4) presentation >24 h post-ingestion.[4,5] Interestingly, about 3.9%–5.2% of vulnerable acetaminophen-poisoned patients have been shown to develop LI despite NAC administration.[5–7] In contrast, other patients at lower risk of hepatotoxicity may receive NAC by excess, resulting in a significant increase in bed occupancy and potentially preventable NAC-related adverse events.[5,8,9] To date, the identification of such patients cannot be achieved based on the nomogram only.

Therefore, asides from the nomogram, predictive biomarkers are needed to early identify, among acetaminophen-poisoned patients receiving NAC, those at risk of LI.[5,10] These patients may consequently benefit from closer clinical and laboratory monitoring, prolonged or higher doses of NAC, and earlier decision of liver transplantation if needed. Conversely, decision against NAC treatment or a short regimen, as well as rapid discharge, may be safely proposed in patients at lower risk of LI. For this purpose, novel biomarkers have been developed, such as acetaminophen protein adducts and liver micro-RNAs (miR-122) or proteins (HMGB1, keratin 18, and GLDH).[5,11,12] However, further evaluation is needed and these biomarkers are still not available in routine practice.[5,10,12]

The liver has been suggested as a potential source of production of procalcitonin (PCT),[13] a readily and commonly used validated biomarker of bacterial infection[14,15]. We sought to investigate its contribution to identifying, upon admission, acetaminophen-poisoned patients likely to develop LI.

Key points

1. Summarize the established knowledge on this subject
- For decades, a nomogram has been used to predict acetaminophen-induced hepatotoxicity
- Nevertheless, using the nomogram has not been validated in several common scenarios, including chronic overdose or when time from ingestion to presentation is unknown
- New biomarkers that would complement the nomogram for patient stratification are needed

2. What are the significant and/or new findings of this study?
- In 117 prospective patients, plasma procalcitonin on admission was associated to liver injury with excellent accuracy and negative predictive value
- The rise of plasma procalcitonin preceded that of alanine aminotransferase by a median of 33 h
- Plasma procalcitonin on admission may help in early identification of patients at higher or lower risk of ALI in whom personalized management may be used

PATIENTS & METHODS

This study was performed in accordance with the ethical standards of the Ethics Committee of the French Society of Intensive Care Medicine (FICS) and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16] The study protocol was declared to the National Commission on Informatics and Liberty (CNIL) and approved by the FICS Ethics Committee (CE SRLF 18-14). Participating patients were informed, but written consent was waived due to the observational methodology of the study.

Patient population and poisoning management

In this prospective observational cohort study, we included all consecutive acetaminophen-poisoned patients admitted to the toxicological intensive care unit of a University Hospital in Paris, France, between January 2012 and December 2017.

Plasma PCT, C-reactive protein (CRP), liver and coagulation tests, blood lactate, and plasma acetaminophen concentrations were systematically measured on admission. As part of routine clinical follow-up, subsequent blood tests were performed at the discretion of the treating physician. Plasma PCT was measured using a Cobase® automated analyzer (Roche, normal, <0.05 ng/ml). Plasma acetaminophen concentration was measured using a spectrophotometric method (therapeutic range, 5–25 mg/L). Acetaminophen-induced LI was defined as the peak increase in alanine aminotransferase (ALT) >100 IU/L, corresponding to the French indication for continuing NAC therapy after completion of the initial regimen at the time of the

study. Patients were considered for referral to the liver transplantation unit of a neighboring hospital in case of acute liver failure (ALF). ALF was defined as the association of severe LI with encephalopathy and international normalized ratio (INR) >1.5 at any time.[17,18]

NAC was administered in all patients as per French recommendations: (1) baseline plasma acetaminophen concentration above the cutoff (starting at 150 mg/L at the fourth hour post-ingestion according to the Rumack–Matthew nomogram);[4] (2) increased plasma ALT > 50 IU/L; or (3) nonvalidity of the nomogram due to unknown overdose timing, time from ingestion out of the 4–24 h range, chronic overdose or presence of co-ingested toxicants delaying gastrointestinal absorption. All patients received intravenous NAC with a 150 mg/kg loading dose during the first hour, followed by 50 mg/kg and 100 mg/kg during the next 4 and 16 h, respectively. Then, a daily infusion of 300 mg/kg NAC was given until plasma acetaminophen concentration was undetectable and significant liver function improvement was obtained.

Data collection

The following demographic, clinical, biological, and outcome variables were prospectively collected in a dedicated registry: age, gender, weight, history of ethanol abuse and suicide attempt, history of liver, kidney and psychiatric diseases, body temperature, abdominal pain, nausea/vomiting, cardiovascular failure defined as mean arterial pressure <65 mmHg requiring catecholamine administration, Glasgow coma score, and clinical suspicion of associated infection. Toxicological data collected included the presumed ingested acetaminophen dose and time of ingestion whenever available, the type of overdose (acute ingestion or chronic overdose), and the presumed co-ingestions (ethanol, codeine, tramadol, nonsteroidal anti-inflammatory drugs, psychotropic, and cardiotoxic drugs). The baseline acetaminophen concentration was considered not interpretable in case of co-ingestion of drugs potentially delaying acetaminophen gastrointestinal absorption such as codeine and tramadol. Time to NAC administration was defined as the delay from the presumed time of acetaminophen ingestion to the time of NAC administration. Laboratory data collected on admission included plasma CRP, PCT acetaminophen, ethanol, liver function and coagulation tests, serum creatinine, and blood lactate. The time course of ALT, PCT, CRP, INR, and lactate values were recorded if available. Management and follow-up data collected included charcoal administration, mechanical ventilation, length of ICU stay, referral to the liver transplantation unit, and death.

Statistical analysis

Quantitative data were reported as medians (interquartile range). Normally distributed quantitative data were analyzed using Student *t*-tests. The Mann–Whitney U-tests or Wilcoxon Sum-Rank tests were used otherwise. Qualitative data were reported as the number of patients (percentages) and compared using Pearson $\chi 2$ tests or Fisher exact tests, depending on the sample size. The value of PCT on admission for the diagnosis of LI was assessed using the receiver-operating characteristics (ROC) curve, sensitivity, specificity, accuracy, negative, and positive predictive value. The estimated area under the ROC curve (95% confidence interval [CI]) was computed. The Youden index was used to determine the optimal threshold of PCT concentration in terms of sensitivity and specificity. PCT variable was then dichotomized for testing in univariate and multivariate analysis.

Multivariate analysis of the association between PCT levels and LI was performed using a Cox proportional-hazards regression model including all variables with *p*-values <0.10 in univariate analysis. Age, history of chronic liver disease, delay to NAC administration, and clinical suspicion of infection were planned to be included in the Cox regression model to adjust on potential confounding factors. Results of the multivariate analysis are shown as hazard ratio (HR) with their 95%CI. Incidence of LI according to admission PCT value was presented as Kaplan Meier curves.

All tests were two-sided. Missing data were not analyzed or estimated. *p-values* <0.05 were considered to be significant. Analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Patient characteristics

A total of 117 consecutive patients (86 female [74%]/31 male [26%]; age, 32 years [21–53]) were included after the ingestion of a median amount of 16 g (9–30) of acetaminophen. Baseline and follow-up patient characteristics are described in Table 1. Poisoning resulted from suicide attempt in 110 patients (94%). Poisoning involved co-ingested drugs in 90 cases (77%), including benzodiazepines in 35 (30%), codeine in 34 (29%), tramadol in 18 (10%), nonsteroidal anti-inflammatory drugs in 16 (14%), and other psychotropic drugs in 48 (41%) patients. The nomogram was considered as noninterpretable in 55 patients (47%) due to unknown or >24 h time of ingestion in 36/55 (65%), chronic overdose in 7/55 (13%), or tramadol/codeine co-ingestion in 12/55 (22%) patients. The delay from ingestion to NAC administration was 6 h (4–12) (available data, $N = 88$). Biochemical tests on presentation included serum ALT of 29 IU/L (14–99), bilirubin of 9 µmol/L (6–17), serum ALP of 68 IU/L (52–87), serum GGT of 24 IU/L (16–49), INR of 1.2 (1.1–1.4), and serum creatinine of 62 µmol/L (53–82).

On admission, 32 patients (27%) were comatose and 22 (19%) patients presented with cardiovascular failure, due to ALF in seven patients or due to co-ingested drugs otherwise. Bacterial infection was suspected in 28 patients (24%) upon admission, consisting of 23 aspiration pneumonia, 4 urinary tract infections, and 1 colitis with no significant difference in patients with or without LI. Infection was eventually confirmed during the follow-up in 23 of them, with

TABLE 1 Characteristics of the 117 acetaminophen-poisoned patients

	Liver injury *n* = 38 (%)	No liver injury *n* = 79 (%)	Overall population *n* = 117 (%)	*p*-value
Age, years[a]	41 (24–55)	28 (20–49)	32 (21–53)	0.04
Female	29 (76)	57 (72)	86 (74)	0.63
Weight, kg[a]	68 (56–75)	67 (59–78)	68 (59–76)	0.77
History of chronic diseases				
Alcohol abuse	5 (13)	7 (9)	12 (10)	0.52
Liver disease	2 (5)	1 (1)	3 (3)	0.25
Psychiatric illness	28 (74)	58 (73)	86 (74)	0.98
Acetaminophen overdose				
Presumed ingested dose, g[a]	24 (13–31)	16 (8–30)	16 (9–30)	0.12
Suicide attempt	34 (90)	76 (96)	110 (94)	0.21
Delay to NAC administration, h[a,b]	15 (8–23)	5 (4–8)	6 (4–12)	<0.01
Co-ingested drugs	29 (76)	61 (77)	90 (77)	0.91
Nomogram uninterpretable	18 (47)	37 (47)	55 (47)	0.40
Clinical data				
Abdominal pain	10 (26)	12 (15)	22 (19)	0.15
Nausea/Vomiting	15 (40)	33 (42)	48 (41)	0.81
Cardiovascular failure	13 (34)	9 (11)	22 (19)	<0.01
Glasgow coma score <8	14 (37)	18 (23)	32 (27)	0.11
Suspicion of infection on admission	16 (20)	12 (32)	28 (24)	0.18
Biological data[a]				
Admission acetaminophen, mg/ml	41 (12–133)	53 (22–137)	51 (21–133)	0.35
Admission creatinine, µmol/L	77 (56–127)	61 (51–73)	62 (53–82)	<0.01
Admission ALT, IU/L	297 (99–1433)	18 (12–32)	29 (14–99)	<0.001
Peak ALT, IU/L	2020 (577–4248)	21 (15–36)	33 (18–555)	<0.001
Admission bilirubin, µmol/L	13 (8–34)	8 (6–14)	9 (6–17)	0.001
Admission ALP, IU/L	78 (63–106)	61 (48–81)	68 (52–87)	0.005
Admission GGT, IU/L	44 (20–134)	22 (14–38)	24 (16–49)	0.002
Admission INR	1.5 (1.3–2.7)	1.1 (1.1–1.3)	1.1 (1.2–1.4)	<0.001
Admission C-reactive protein, mg/L	7 (4–23)	4 (4–4)	4 (4–8)	<0.01
Admission lactate, mmol/L	2.1 (1.2–6.6)	2.0 (1.1–2.8)	2.0 (1.2–3.3)	0.10
Admission PCT, ng/ml	21.5 (3.0–45.3)	0.1 (0.0–0.4)	0.2 (0.1–10.8)	<0.001
Admission PCT > 1 ng/ml, *n* (%)	33 (87)	13 (17)	46 (39)	<0.01
ICU management				
Activated charcoal	6 (16)	14 (18)	20 (17)	0.79
Mechanical ventilation	10 (26)	8 (10)	18 (15)	0.02
Length of ICU stay, days[a]	5 (2–9)	2 (1–3)	2 (1.5–4.5)	<0.01
Non-survivors	8 (21)	1 (1)	9 (8)	<0.01

Abbreviations: ALT, alanine aminotransferase; ICU, intensive care unit; INR, international normalized ratio; NAC, N-acetylcysteine; PCT, procalcitonin.

[a]Median (interquartile range).

[b]Delay to NAC administration was calculated from the time of ingestion if known (*N* = 88).

microbiology diagnosis obtained in six patients only. Mechanical ventilation was required in 18 patients (15%) with a median duration of 3 days (0.8–6). The median length of ICU stay was 2 days (1.5–4.5). Nine patients (8%) died. The reason for death was ALF in eight patients and cardiogenic shock in one patient.

Predictive value of admission PCT for the diagnosis of LI

LI occurred in 38 patients (32%) including 27 patients on admission and 11 during the follow-up period, with a median peak serum ALT of 2020 IU/L (577–4248). In 29 patients (25%), LI progressed to ALF, with complete recovery during the follow-up in 18/29 (62%) patients, liver transplantation request in 3/29 (10%), and death in 8/29 (28%) patients. Median plasma PCT concentration on admission was 0.2 ng/ml (0.1–10.5) and was significantly higher in patients with LI (21.5 ng/ml [3.2–44.9] versus 0.1 ng/ml [0–0.4], $p < 0.001$); Figure 1). ROC analysis of the plasma PCT concentration on admission to discriminate between LI and non-LI patients showed AUC of 0.91 (95%CI: 0.84 to 0.97) (Figure 2). The optimal threshold value for PCT was 0.96 ng/ml, with sensitivity, specificity, accuracy, negative, and positive predictive values of 92%, 84%, 86%, 96%, and 73%, respectively.

Based on univariate analyses, age ($p = 0.04$), delay to NAC administration ($p < 0.01$), cardiovascular failure ($p < 0.01$), serum creatinine ($p < 0.01$), plasma CRP ($p < 0.01$), and plasma PCT > 1 ng/ml ($p < 0.01$) were significantly associated with increased incidence of LI (Table 1). Despite slight elevation (2.0 mmol/L [1.2–3.3]; *N*: 0.5–1.6), no significant association was found between blood lactate concentration on admission and LI ($p = 0.10$). Among the 16 patients who had blood lactate concentration >3 mmol/L on admission, none of them progressed to LI or cardiovascular failure and lactate returned to normal values within 12 h delay (10–30).

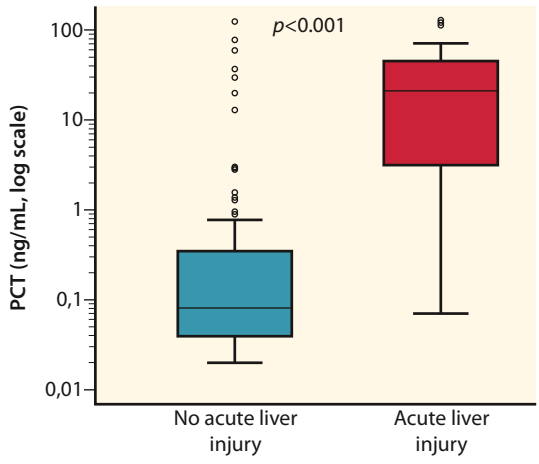

FIGURE 1 Plasma PCT concentrations on admission according to the onset of liver injury in 117 acetaminophen-poisoned patients. log, logarithmic; ng/ml, nanograms per milliliters; PCT, procalcitonin

After adjustment in the Cox regression model (Table 2), admission PCT concentration >1 ng/ml was independently associated with increased onset of LI (HR: 7.2 [95%CI: 2.3–22.6]; $p < 0.001$; Figure 3), as was the delay to NAC administration (HR: 1.03 [95%CI: 1.0–1.1]; $p = 0.04$). Among the 11/38 patients who developed LI during the follow-up despite NAC, the increase in PCT > 1 ng/ml preceded the increase in ALT by 33 h (10–74; Figure 4). In the subgroup of 38 patients with LI, median PCT was 21.6 (4.5–42.5) ng/ml in patients with LI + ALF versus 9.2 (0.4–50.4) ng/ml in patients with LI alone ($p = 0.49$).

Admission PCT significantly correlated with peak serum ALT (rs = 0.58, $p < 0.001$) and the delay to NAC administration (rs = 0.54, $p < 0.001$).

DISCUSSION

In this observational cohort including 117 acetaminophen-poisoned patients treated by NAC, with 38 cases of LI, we suggest that plasma PCT concentration on admission may be an early independent predictor of LI with an excellent accuracy and negative predictive value. The rise in PCT in acetaminophen-induced LI patients was particularly high (median value, 21.5 ng/ml), much greater than the 1–2 ng/ml cutoff commonly used to identify bacterial infections.[14] Such elevated values are generally observed in septic shock.[19] Interestingly, the rise in PCT tended to be higher in patients with LI + ALF (median 21.6 ng/ml) than in patients with LI alone (median 9.2 ng/ml). However, the difference did not reach statistical significance.

Our findings support a remarkable association between PCT and acetaminophen-related LI. First and foremost, despite the increasing clinical interest for PCT in the setting of sepsis,[14,20] its tissue production source remains poorly understood. Although primarily identified in thyroid-C-cells and neuroendocrine cells,[21,22] data suggest that the liver is a potential source of sepsis-related PCT production, as PCT mRNAs have been found to be highly expressed in the hepatic tissue.[13] Second, in an attempt to better predict bacterial infection in the setting of liver disease, recent investigations with plasma PCT monitoring reported uncommonly elevated PCT concentrations in numerous LI and ALF patients, with no or poor cutoff values for the diagnosis of infection.[23–29] These findings suggested a strong association between PCT increase and LI, while hampering its diagnostic value for sepsis in this setting.[29] Consistent with our results, Jackson et al. found high PCT concentrations in acetaminophen-induced ALF [median value, 9.4 ng/ml (0.9–123.8)].[30] Similar cases were recently published.[31] Moreover, Mallet et al. reported significantly higher PCT concentrations in acetaminophen-induced ALF than in any other causes (10.6 vs. 0.8 ng/ml $p < 0.0001$), irrespective of any concurrent infection (10.3 vs. 10.7 ng/ml, $p = 0.7$).[32] In a pediatric cohort study, Tschiedel et al. observed that paracetamol intoxication led to a marked increase in PCT serum levels, correlating with ALT but not correlating with the INR or paracetamol blood levels, consistent with our findings.[33]

Interestingly in our study, the rise of PCT levels preceded that of ALT by a median of 33 h in patients with normal ALT on admission.

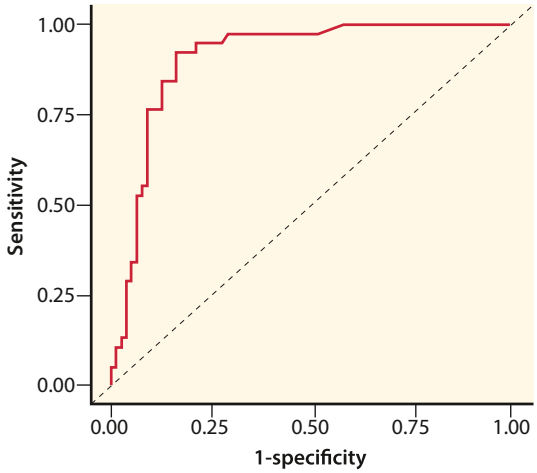

FIGURE 2 Value of plasma PCT concentration on admission in the diagnosis of liver injury in the acetaminophen-poisoned patient (receiver-operating characteristics curve). AUC, area under the ROC curve; CI, confidence interval; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value
Legend table

PCT best cutoff value	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)	Youden index (95%CI)	AUC (95%CI)
0.96 ng/ml	0.92 (0.79–0.98)	0.84 (0.74–0.90)	0.86 (0.78–0.92)	0.73 (0.58–0.85)	0.96 (0.88–0.99)	0.76 (0.64–0.88)	0.91 (0.84–0.97)

TABLE 2 Risk of liver injury in 117 acetaminophen-poisoned patients based on a multivariate Cox proportional hazard model

	Multivariate analysis[a]		
	p-value	HR	95%CI
Age, years	0.94	-	-
History of liver disease	0.06	-	-
Delay to NAC administration, h_2	**0.04**	**1.03**	**1.0–1.1**
Cardiovascular failure	0.79	-	-
Clinical suspicion of infection	0.45	-	-
Plasma C-reactive protein, mg/L	0.56	-	-
Serum creatinine, µmol/L	0.71	-	-
Plasma procalcitonin >1 ng/ml	**<0.001**	**7.2**	**2.3–22.6**

Note: Bold values indicate significant results.

Abbreviations: CI, confidence interval; HR, hazard ratio; NAC, N-acetylcysteine.

[a]The multivariate analysis included 83 complete cases.

[b]Delay to NAC administration was calculated from the time of ingestion if known (available data $N = 88$).

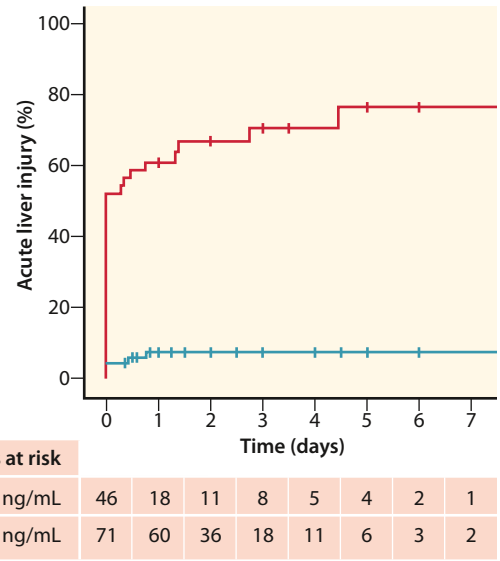

FIGURE 3 Probability of acetaminophen-induced liver injury according to admission PCT concentration (Kaplan–Meier curves, $p < 0.001$). PCT, procalcitonin

Moreover, the association between PCT levels and LI was independent from and stronger than the delay to NAC administration, which is the most recognized risk factor for the development of hepatotoxicity and mortality in the setting of acetaminophen poisoning.[4,5,34] Plasma PCT concentrations could be even more useful when the nomogram is not interpretable, as the ingestion time is frequently unknown or unreliable.[35] Over the years, several prognostic tools have been developed to identify patients more likely to die without liver transplantation. In this regard, the King's College Hospital and Clichy Criteria have been validated and used worldwide in combination with blood lactate >3 mmol/L. However, they are only useful once ALF is established.[36,37] Interestingly, at the early stages of poisoning, we observed a slight increase in blood lactate but no significant association with LI or cardiovascular failure and a rapid

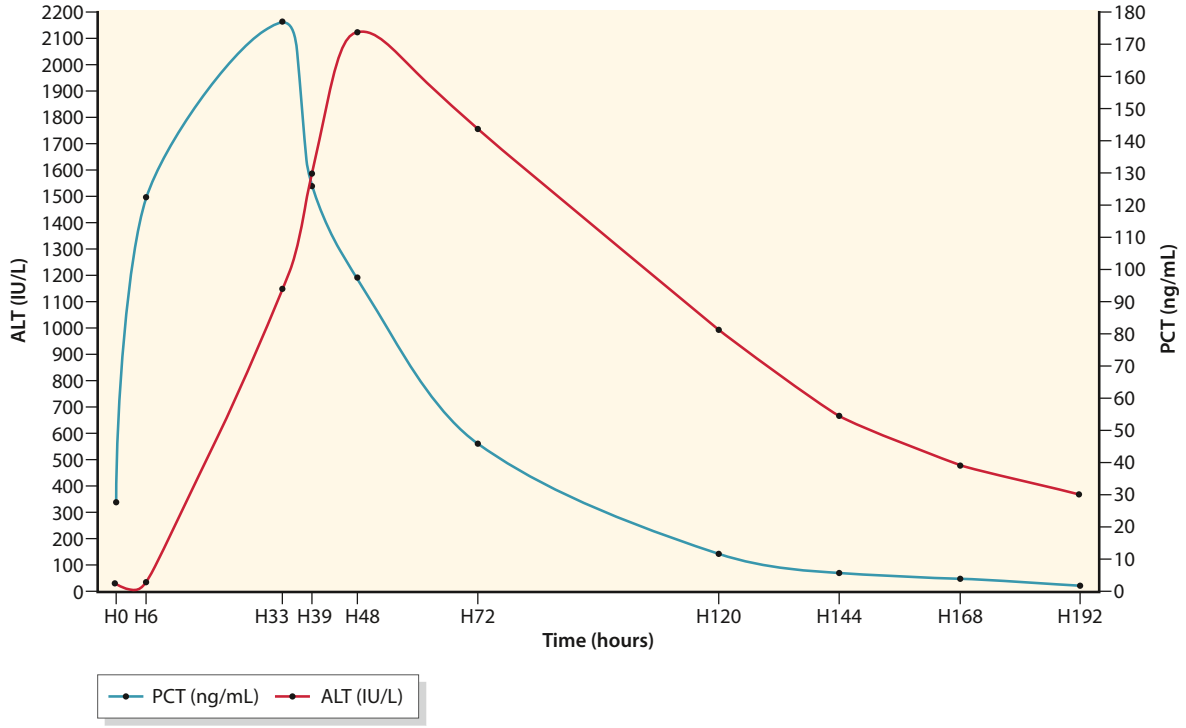

FIGURE 4 Time course of plasma PCT and ALT concentrations in an acetaminophen-poisoned patient. This 90-year-old woman was admitted 16 h post-ingestion of an unknown dose of paracetamol. On admission, she presented with high acetaminophen plasma levels 136 mg/ml, high procalcitonin levels 27 ng/ml, and normal liver tests. ALT, alanine aminotransferase; PCT, procalcitonin

normalization within a median delay of 12 h. None of the patients with baseline lactate >3 mmol/L progressed to LI or ALF. This observation is consistent with studies suggesting a direct inhibitory toxic effect of acetaminophen on cellular respiration in mitochondria[38,39] and with other reports of severe overdose presenting early with lactic acidosis without overt signs of hepatic damage or shock.[39–41]

Acetaminophen poisoning is a common etiology for emergency room admission resulting in significant bed occupancy (around 47,000 bed days per year in the United Kingdom).[12,42] Management is only based on the interpretation of admission acetaminophen concentration on the nomogram. As a result, numerous patients may be over-treated with a time-consuming and potentially harmful antidote, especially since the toxic threshold has been recently lowered in some countries such as the United Kingdom.[5] Minor adverse reactions to NAC have been reported in 15%–45% of treated patients, mainly including nausea, vomiting, and anaphylactoid reactions. Additionally, although rare, some fatalities have been reported.[8,9] On the other hand, patients at higher risk of LI may be undertreated, with a small subgroup of patients that will develop liver toxicity despite appropriate therapy.[5] Therefore, the burden of overdose and limitations of current management have led to a particular interest in new biomarkers that would complement the nomogram for the early identification and discrimination of patients at high or low risk of LI. High-risk patients may benefit from closer monitoring, earlier recognition of ALF, and appropriate listing for liver transplantation. Conversely, low-risk patients may safely be offered abbreviated NAC regimen or early discharge.[5,12] However, and contrary to PCT which can be rapidly and accurately measured by point-of-care testing, none of the promising biomarkers recently highlighted is readily available in daily clinical practice.[5,12]

Some limitations of our study should be underlined. First, our primary outcome was an increase in ALT > 100 IU/L. Although lower than the threshold used in the published definition of drug-induced LI, ALT > 100 IU/L is commonly used in toxicological risk stratification studies of acetaminophen-poisoned patients.[12,43] Besides, this cutoff is widely used in the French and UK clinical guidelines (www.toxbase.org) to indicate the need for further NAC treatment, based on evidence that substantial LI is unlikely if serum ALT is <100 IU/L.[7] Green et al. showed that 97% of the patients with peak serum ALT > 1000 IU/L exhibited ALT > 100 IU/L at the end of the 21 h NAC treatment.[7] Second, an important proportion of our patients ingested other drugs that may have caused specific hepatotoxicity, interactions with acetaminophen metabolism, or systemic consequences (such as cardiovascular failure, kidney injury, systemic inflammation or infections) affecting both ALT and PCT levels. However, this heterogeneity reflects the real-life clinical epidemiology of acetaminophen poisoning in France, and the multivariate analysis adjusted on these potential confounding factors. Besides, high rates of drug co-ingestions were reported in a large recent US cohort of 1162 patients with acetaminophen-induced LI.[44] Third, the

delay from the PCT rise to the ALT rise was only evaluated in the 29% of LI patients who had presented with normal liver tests and developed hepatotoxicity during follow-up. Finally, given our findings are based on a monocentric and tertiary care cohort study, interpretation should be cautious. More studies are required to confirm the added value of PCT in the setting of acetaminophen poisoning as well as in other causes of LI.

CONCLUSION

Our results suggest that high plasma PCT on admission is independently associated with LI and may be an early predictor of LI in the setting of acetaminophen poisoning. PCT measurement may help in earlier identification of patients at higher or lower-risk of LI in whom personalized management and adapted NAC regimen may be used. Our findings should be validated in future prospective large-cohort studies.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Study concept and design: Alexandre Nuzzo, Eric Vicaut, and Bruno Mégarbane. Acquisition of data: Alexandre Nuzzo, Shireen Salem, Hervé Gourlain, and Bruno Mégarbane. Analysis and interpretation of data: Alexandre Nuzzo, Abdourahmane Diallo, Eric Vicaut, Sebastian Voicu, and Bruno Mégarbane. Drafting of the manuscript: Alexandre Nuzzo and Bruno Mégarbane. Critical revision of the manuscript for important intellectual content: Antoine Goury, Isabelle Malissin, Nicolas Deye, Nicolas Péron, Eric Vicaut, Sebastian Voicu, and Bruno Mégarbane. Statistical analysis: Abdourahmane Diallo and Eric Vicaut. Study supervision: Bruno Mégarbane.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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APPENDIX A STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item no	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(b) For matched studies, give matching criteria and number of exposed and unexposed

(Continues)

APPENDIX A (Continued)

	Item no	Recommendation
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed
		(e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—for example, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarize follow-up time (e.g., average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarize key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

*Give information separately for exposed and unexposed groups.