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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Screening for hazardous alcohol use in the Emergency Department: Comparison of phosphatidylethanol with the Alcohol Use Disorders Identification Test and the Timeline Follow-back

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Abstract

Background: Up to 15% of all visits to the Emergency Department (ED) are alcohol related. Identification of problematic alcohol use is important in this setting because it allows for intervention and prevention efforts. This study investigated the correlation between the objective phosphatidylethanol (PEth) marker and the subjective Alcohol Use Disorders Identification Test (AUDIT) and Timeline Followback Questionnaire (TLFB) as screening methods for hazardous alcohol use in the general ED population.

Methods: This prospective cohort study included 301 ED patients (57% male) who were seen in the ED and required to give a blood sample. The correlation between the values of PEth (PEth 16:0/18:1 and PEth 16:0/18:2) and the scores on the AUDIT and TLFB were analyzed using Spearman's rank correlation coefficient. Differences between risk categories of PEth and AUDIT were also examined.

Results: The Spearman correlation coefficients between PEth 16:0/18:1|PEth 16:0/18:2 values and the AUDIT scores were moderate (PEth 16:0/18:1: 0.67, $p < 0.001$; PEth 16:0/18:2: 0.67, $p < 0.001$). Of the patients who scored 'low risk drinking/abstinence' according to the AUDIT questionnaire, respectively 1% and 4% had PEth 16:0/18:1|PEth 16:0/18:2 values indicating excessive alcohol use, and another 10% and 12% had PEth 16:0/18:1|PEth 16:0/18:2 values indicating moderate alcohol consumption. Of the 12 (PEth 16:0/18:1) and 25 (PEth 16:0/18:2) patients with high-risk values, respectively 25% and 40% scored in the lowest risk category on the AUDIT questionnaire. Spearman correlation coefficients between PEth 16:0/18:1|PEth 16:0/18:2 values and TLFB two-week scores were high (PEth 16:0/18:1: 0.74, $p < 0.001$; PEth 16:0/18:2: 0.82, $p < 0.001$).

Conclusions: AUDIT scores were moderately correlated with PEth values in the general ED population. In almost all cases where there was not a good correlation, patients had high PEth values with low AUDIT scores. We conclude that PEth identifies

Trial Register: Netherlands Trial Register, Trial NL7590.

patients with problematic alcohol use who are missed by the AUDIT questionnaire and therefore PEth could be used as an additional screening method for hazardous alcohol use in this population.

KEYWORDS
alcohol, alcohol use disorders identification test (AUDIT), Emergency Department, intoxications, phosphatidylethanol (PEth)

INTRODUCTION

Hazardous alcohol use is a problem not only affecting the individual but also poses a burden on society, including the medical healthcare system (Verheij et al., 2019). In 2018, 9% of the adult Dutch population met the criteria for heavy drinking and 8% for excessive drinking (Trimbos Insitute, 2019). This hazardous alcohol use may have several harmful effects (Anderson et al., 1993; World Health Organization, 2014). The World Health Organization stated that alcohol is a causal factor in >200 disease and injury conditions and accounts for 6% of all deaths worldwide (World Health Organization, 2014).

Alcohol-related visits are common at the Emergency Department (ED); 12–15% of all attendances were related to alcohol (Parkinson et al., 2016). In certain subgroups these rates were even higher; for example, almost 20% of all trauma patients at the ED reported the consumption of at least three units of alcohol prior to their injury (Rood et al., 2016). A significant proportion of persons who sought medical care either had alcohol problems or consumed alcohol in such a way that it contributed substantially to their actual or potential medical problems (The Institute of Medicine [US] Committee, 1990). Also, alcohol-related ED visits are increasing at a greater rate than overall ED visits and thereby represent a growing burden on hospital resources (Mullins et al., 2017; Verheij et al., 2019).

The ED is important for the early identification of problematic alcohol users (Cherpitel et al., 1996). The Institute of Medicine (US) Committee on Treatment of Alcohol Problems supports this point of view with their statement that they believe that all persons coming for care to medical settings should be screened for alcohol problems and that medical settings are a major site in which the treatment of alcohol problems should be enacted (The Institute of Medicine (US) Committee, 1990). Adequate screening for problematic alcohol use is important because it provides the opportunity for possible intervention or referral (Cherpitel et al., 1996; The Institute of Medicine (US) Committee, 1990).

Over the years, various methods to screen for hazardous alcohol (ab-)use have been used in different clinical settings including breath analyses, indirect markers for alcohol, and different questionnaires (Barata et al., 2017; McGinnes et al., 2016; Nilsen et al., 2008). The Alcohol Use Disorders Identification Test (AUDIT/AUDIT-C for concise/consumption version) is one of the most frequently used validated screening questionnaires (Barata et al., 2017; Bush et al., 1998; Drummond et al., 2014; Neumann et al., 2006; Schippers & Broekman, 2010; Sommers et al., 2006; World Health Organization, 2011).

The AUDIT is developed to screen for excessive drinking and to identify persons with hazardous patterns of alcohol consumption that would benefit from reducing/ceasing their alcohol consumption (World Health Organization, 2011). Another frequently used questionnaire is the Timeline Followback Questionnaire (TLFB); a retrospective self-administered questionnaire for the estimation of daily alcohol consumption over a specific time period prior to the interview (Sobell & Sobell, 1992). However, these questionnaires may entail a risk of response or social desirability bias since they are self-reported measures (Adong et al., 2019). Phospatidylethanol (PEth) is a direct and objective blood marker of chronic alcohol (ab-) use. Since PEth is a metabolite of EtOH, it can only be detected after alcohol use (Viel et al., 2012) and is suggested as an important indicator for chronic alcohol consumption in different contexts such as inpatient and emergency admission (Kiefer et al., 2022). An important difference with other (indirect) markers is that PEth did not seem to be influenced by patient characteristics such as age, gender, and co-morbidity (Viel et al., 2012). The half-life is 4–5 days and PEth could be detected up to two or more weeks, which is an advantage compared to, for example, the urinary metabolite ethyl glucuronide (EtG) which reflects alcohol consumption during the last 72 h (Schröck et al., 2017; van de Luitgaarden et al., 2019; Wassenaar & Koch, 2015).

More than 40 different homologues are discovered. The homologues 16:0/18:1 (PEth 16:0/18:1) and 16:0/18:2 (PEth 16:0/18:2) are the most abundant homologues in human blood (Hahn, Anton, & Javors, 2016; Schröck et al., 2017; Simon, 2018; Wassenaar & Koch, 2015). It is suggested to use both these measures to investigate alcohol use (Hill-Kapturczak et al., 2018).

Several studies examined alcohol use measured by the AUDIT(-C) versus the PEth marker value among different populations and the results underlined the advantages of PEth (Adong et al., 2019; Couture et al., 2016; Francis et al., 2015; Hahn, Emenyonu, et al., 2016; Kip et al., 2008; Piano et al., 2015). Multiple studies showed that there were patients with positive PEth values while scoring negative on the AUDIT(-C) indicating the advantages of PEth as a (additional) screening method to identify problematic alcohol use (Adong et al., 2019; Couture et al., 2016; Eyawo et al., 2018; Ferguson et al., 2020; Hahn, Emenyonu, et al., 2016; Irvin et al., 2020; Papas et al., 2016). Only a few studies examined the use of PEth within a (sub-)population of ED patients, also showing the advantages of PEth in these (sub-) populations (Gerbase et al., 2021; Kip et al., 2008). There are no studies to date that have investigated PEth in the general adult ED population.

The current study aimed to investigate the correlation between the values of PEth and self-reporting on the AUDIT in a large sample of adult patients in the general ED population, including a comparison between the according to risk categories. The secondary aim was to study the correlation between PEth and self-reported alcohol consumption over the past 2 weeks and 24 h (TLFB questionnaire).

MATERIALS AND METHODS

Study design, setting, and selection of participants

This was a comparative study of tests within one population. The ethics committee of the Erasmus MC University Medical Center Rotterdam approved this study (MEC-2017-564). This trial was registered in the Netherlands Trial Register, Trial NL7590. The study population consisted of all adult patients who presented to the ED (regardless of the reason for presentation) and that required blood withdrawal for standard clinical workup (independently of this study). All patients who met these conditions were asked to participate in this study. After informed consent was obtained, patients were asked to complete the AUDIT and the two-week and 24-h TLFB questionnaire, and extra blood was drawn to determine the value of PEth. Exclusion criteria were age <18, language barrier, previous participation in this study, and having a medical condition that made the patient unsuitable for inclusion (for example too ill to obtain informed consent/fill in questionnaires, unconscious or intubated patients). Patients who were intoxicated with alcohol and/or other drugs or substances at presentation could participate in this study if they stayed in the ED long enough to detoxify in such a matter that they were fully mentally competent and informed consent could be obtained. Inclusions took place from March–May 2019 during 12-h periods (day/night shifts starting at 08.00 AM/PM). Day shifts were performed three times on a Monday–Saturday and twice on Sunday. All night-shifts were performed three times on Tuesday–Saturday and twice on Monday and Sunday.

Measurements

Alcohol use disorders identification test

The AUDIT is one of the most frequently used screening questionnaires (Drummond et al., 2014; Neumann et al., 2006; Sommers et al., 2006; World Health Organization, 2011). The questions address different areas; alcohol consumption, alcohol dependence and alcohol-related problems. The number of points determines the risk level by zones and the corresponding intervention advice. Zone 1 (0–7 points) is 'low risk drinking/abstinence' with advice 'alcohol education'. Zone 2 (8–15 points) is 'medium level of alcohol problems' with intervention advice 'simple advice'. Zone 3 (16–19 points) and 4 (20–40 points) are both 'high level of alcohol problems' with the intervention advises 'simple advice plus brief counselling and continued monitoring' and 'referral to specialist for diagnostic evaluation and treatment' respectively. The original AUDIT is a validated screening test, specifically designed for international use (World Health Organization, 2011). Also, a shortened version, the AUDIT-C, containing the first three questions of the AUDIT regarding consumption, can be used (Bush et al., 1998). A Dutch translation was used for the current study (Schippers & Broekman, 2010).

Timeline followback questionnaire

The TLFB is a self-administered questionnaire for assessing the quantitative recent drinking behavior. Patients are asked to retrospectively estimate their daily alcohol consumption over a time period prior to the interview. One standard drink corresponds with 13.6 g of pure alcohol. For this study, a two-week and 24-h questionnaire was obtained (Sobell & Sobell, 1992).

PEth

The analysis for the PEth values was carried out with UPCC on a Waters Acquity UPC2-MS/MS system consisting of an Acquity UPC2 system, connected to a Waters TQ-S micro triple quadrupole mass spectrometer (Waters Corp, Milford, MA). The PEths (PEth 16:0/18:1 and PEth 16:0/18:2) were purchased from Echelon Bioscience Inc (Salt Lake City, UT). To minimalize the possibility of impurity, different batch numbers were used. The analysis is validated according to FDA/EMA validation guidelines (van der Nagel et al., 2018) and the assay is performed in the ISO15189 accredited Erasmus MC pharmacy laboratory. Based on PEth, three categories of drinking are identified; (1) light drinking/abstinence, (2) moderate alcohol consumption, and (3) excessive drinking. For PEth 16:0/18:1 a level below 20 μg/L is considered to be an indicator of light drinking habits or abstinence; 20–200 μg/L is considered to be an indicator of moderate alcohol consumption and a value >200 was considered to be an indicator of excessive drinking (Ulwelling & Smith, 2018). For PEth 16:0/18:2 a level below 10 μg/L is considered to be an indicator of light drinking habits or abstinence; 10–67 μg/L is considered to be an indicator of moderate alcohol consumption and a value above 67 μg/L was considered to be an indicator of excessive drinking (Schröck et al., 2017).

Other variables

Demographic variables (age, gender) were retrieved from the medical records. Also, information about the reason for attendance (appurtenant medical specialty and whether the reason was an intoxication) was obtained.

Sample size calculation

Based on previous studies it was assumed that the prevalence of hazardous and problematic alcohol use among adult ED patients is 20% (Gerbase et al., 2021; Parkinson et al., 2016; Rood et al., 2016; Schröck et al., 2017; Trimbos Insitute, 2019). PEth has a sensitivity of 92–100% and a specificity of 64–85% (Francis et al., 2015). With an assumed sensitivity of 96% and specificity of 75% and a precision of 5%, the current study required sample size of 301 patients (Bujang & Adnan, 2016; Naing, 2004).

Statistical analysis

The data were extracted and analyzed using SPSS (IBM Corp. 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Demographic characteristics were described using descriptive statistics. To determine the heterogeneity of the studied group, the reasons for attendance were subdivided into appurtenant medical specialties. If the patients were primarily seen by an emergency physician, an appurtenant medical specialty according to their reason for attendance was noted.

The scores of the AUDIT, TLFB two-week and 24-h questionnaires and the PEth values (PEth 16:0/18:1 and PEth 16:0/18:2) were calculated. Also, the scores per zone of the AUDIT were presented. Results were presented for AUDIT zone I–IV and also for zones III and IV combined since both represent 'High level of alcohol problems'. The Shapiro–Wilk test of normality was calculated for each outcome measure to test for the normality of the depend on variables. If scores/values were not normally distributed, medians and percentiles were given. The Kruskal–Wallis test was used to detect differences between the PEth values and the AUDIT zones and TLFB two-week scores. To determine the distribution of the PEth 16:0/18:1 and PEth 16:0/18:2 values/categories and the total AUDIT scores/zones, scatterplots were calculated and distribution was examined. The correlation between the PEth value (μg/L) and the scores on the AUDIT (total score), AUDIT-C, and the TLFB questionnaire (two-week & 24 h) were analyzed using Spearman's rank correlation coefficient. A correlation of 0.7–1.0 was interpreted as a high correlation, 0.5–0.7 as a moderate correlation, and 0.3–0.5 as a low correlation. Any missing data were described. Multivariate linear regression analysis was performed to determine associations between age, gender, AUDIT total score, TLFB (two-week & 24-h), and the PEth 16:0/18:1 and PEth 16:0/18:2 values.

RESULTS

A total of 860 patients were eligible for inclusion. Of these patients, 472 patients were excluded. Of all approached patients, 85 patients refused to participate in the current study. A total of 303 patients were included. The blood samples of two included patients were stored under the wrong temperature conditions and were therefore excluded leaving a study sample size of 301 patients (Figure 1). The study population consisted of 57% males and the mean age was 56 years (Table 1).

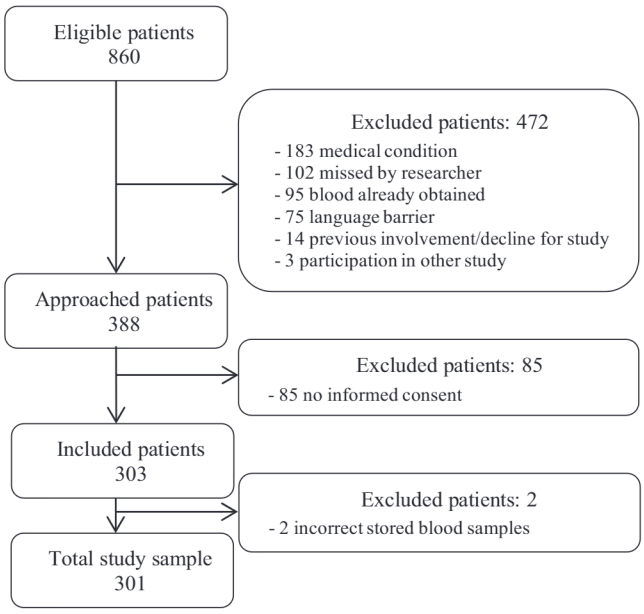

FIGURE 1 Flowchart study sample.

TABLE 1 Demographic and patient characteristics of study population

N	301	
Male (%)	56.8%	
Mean age	55.8 (SD 15.5)	
Reason of attendance: appurtenant medical specialties	Cardiology	21.6%
	Surgery incl trauma	11.6%
	Gastro-enterology	10%
	Pulmonology	8.3%
	Neurology	7.6%
	Oncology	7.3%
	Hematology	6.3%
	Other	<5%
Reason of attendance is intoxication	0.3%	

PEth values, AUDIT scores, and TLFB scores

The range of values for PEth 16:0/18:1 and PEth 16:0/18:2 was large, up to respectively values of 1495 and 1298 μg/L with overall median values of 0. The Shapiro Wilk test showed that all outcome measures (AUDIT total score, AUDIT zone, PEth 16:0/18:1, and PEth 16:0/18:2 values and TLFB 24-h and two-week scores) were not normally distributed (all $p < 0.001$). According to the PEth 16:0/18:1|PEth 16:0/18:2 values, respectively 18% and 22% of the patients had values indicating moderate or excessive alcohol use of

which respectively 23% and 38% had values indicating excessive alcohol use. The correlation between the PEth 16:0/18:1 marker and PEth 16:0/18:2 marker in the total group was 93% (Spearman's test; $p < 0.001$). The median AUDIT score of all patients was 2.0 (range 0.0–30.0). According to the AUDIT, 12% of all patients had scores indicating some level of alcohol problems (medium or high; zone II–IV) of which 23% had scores compatible with a high level of alcohol problems (zone III + IV). The overall median scores for the TLFB two-week questionnaire and 24-h questionnaire were 0 but with wide ranges of up to respectively 168 consumptions during the two-week period and 12 consumptions during the last 24-h period (Table 2).

PEth values versus AUDIT scores

The PEth 16:0/18:1 and PEth 16:0/18:2 values were significantly higher in patients who had a higher zone according to their AUDIT (Kruskal–Wallis Test; $p = 0.000$; Figure 2). Spearman correlation coefficient between the PEth 16:0/18:1 and PEth 16:0/18:2 values and the AUDIT scores were moderate (PEth 16:0/18:1: 0.67, $p < 0.001$; PEth 16:0/18:2: 0.67, $p < 0.001$). The Spearman correlation coefficient between the PEth 16:0/18:1|PEth 16:0/18:2 values and the AUDIT-C scores were also moderate (PEth 16:0/18:1: 0.68, $p < 0.001$; PEth 16:0/18:2: 0.69, $p < 0.001$). For subgroups based on gender, the correlations between PEth 16:0/18:1 and PEth 16:0/18:2 values and AUDIT scores were also moderate; 0.66 and 0.60 for PEth 16:0/18:1 and 0.66 and 0.63 for PEth 16:0/18:2 for respectively males and females. All correlations were significant (Spearman's test; $p = 0.000$). The comparison of the PEth 16:0/18:1 and PEth 16:0/18:2 risk categories versus the AUDIT zones are shown in Table 3.

Of the 266 patients with 'low risk drinking/abstinence' (zone 1) according to the AUDIT, respectively 1% and 4% had high PEth 16:0/18:1/PEth 16:0/18:2 values indicating excessive alcohol use, and another 10% and 12% had PEth 16:0/18:1|PEth 16:0/18:2 values indicating moderate alcohol consumption. Of the patients with 'high level of alcohol problems' (zone III–IV) according to the AUDIT, respectively 75% and 88% showed high PEth 16:0/18:1|PEth 16:0/18:2 values indicating excessive drinking. One patient had a moderate PEth 16:0/18:1 value with a high PEth 16:0/18:2 value and one patient had a 'high level of alcohol problems' according to the AUDIT but showed low values of PEth 16:0/18:1|PEth 16:0/18:2.

Of the patients with high PEth 16:0/18:1|PEth 16:0/18:2 values indicating excessive drinking, respectively 50% and 28% showed a 'high level of alcohol problems' (zone III + IV) according to the AUDIT. Of the 12 patients with high-risk PEth 16:0/18:1 values, three patients (25%) scored in the lowest zone (I) on the AUDIT and another 3 (25%) patients scored 'medium level of alcohol problems' (zone II). Of the 25 patients with high-risk PEth 16:0/18:2 values, 10 patients (40%) scored in the lowest zone (I) on the AUDIT and another 8 (32%) patients scored 'medium level of alcohol problems' (zone II)

TABLE 2 Median AUDIT scores, TLFB scores & PEth marker values; total and by AUDIT zone

	n	AUDIT (median, IQR, range)	TLFB 2 weeks[g] (median, IQR, range)	TLFB 24 h (median, IQR, range)	PEth 16:0/18:1 (μg/L) (median, IQR, range)	PEth 16:0/18:2 (μg/L) (median, IQR, range)
Total	301	2.0 0.0–4.0 0.0–30.0	0.0 0.0–3.5 0.0–168.0	0.0 0.0–0.0 0.0–12.0	0.0 0.0–9.4 0.0–1495.0	0.0 0.0–7.1 0.0–1298.0
AUDIT zone I[a]	266	1.0 0.0–3.0 0.0–7.0	0.0 0.0–2.0 0.0–56.0	0.0 0.0–0.0 0.0–9.0	0.0 0.0–6.1 0.0–375.8	0.0 (0.0–3.8) 0.0–264.7
AUDIT zone II[b]	27	9.0 8.0–13.0 8.0–15.0	17.0 (0.0–36.0) 0.0–102.0	0.0 (0.0–2.0) 0.0–5.0	28.6 (6.6–139.6) 0.0–1495.0	18.1 3.3–120.3 0.0–1298.0
AUDIT zone III[c]	5	17.0 17.0–18.0 17.0–18.0	48.0 16.5–51.5 0.0–54.0	0.0 0.0–2.0 0.0–2.0	242.5 38.2–399.9 0.0–403.7	218.4 37.1–353.3 0.0–466.0
AUDIT zone IV[d,e]	3	29.0 23.0–30.0	45.0 40.0–168.0	4.0 0.0–12.0	1324.0 377.5–1493.0	1248.0 408.8–1265.0
AUDIT zone III + IV[f]	8	18.0 17–27.5 17.0–30.0	46.5 34.75–52.75 0.0–168.0	1.0 (0.0–3.5) 0.0–12.0	386.8 (117.9–1093.9) 0.0–1493.0	324.7 (110.3–1052.5) 0.0–1265.0

[a]AUDIT score 0–7 points; low risk drinking/abstinence.
[b]AUDIT| score 8–15 points; medium level of alcohol problems.
[c]AUDIT score 16–19 points; high level of alcohol problems.
[d]AUDIT score 20–40 points; high level of alcohol problems.
[e]Due to the small group size, IQR could not be calculated.
[f]Zone III + IV combined.
[g]Number of standard drinks in last 2 weeks.

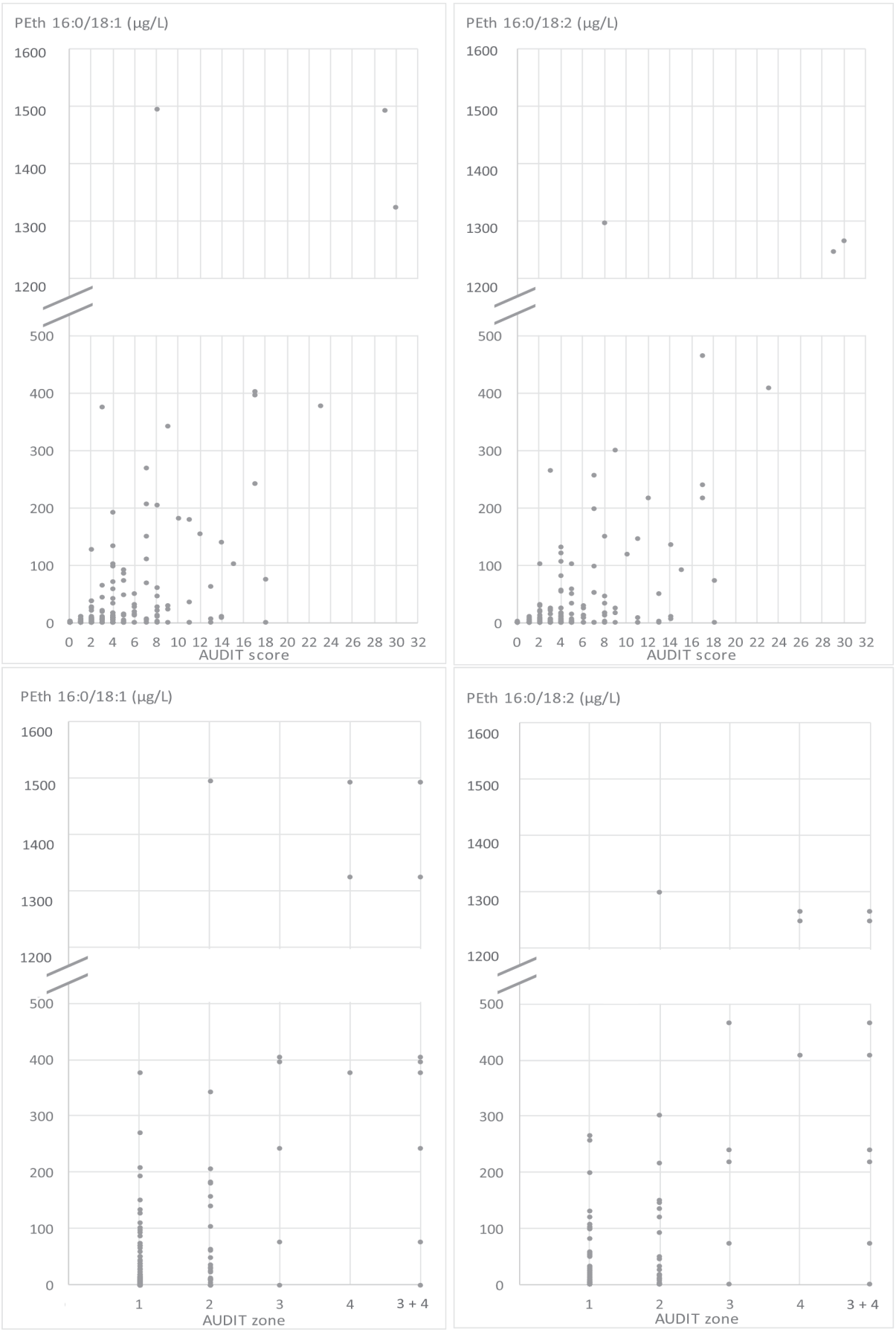

FIGURE 2 Distribution of AUDIT scores/zones[a] versus PEth 16:0/18:1 and PEth 16:0/18:2 values. *Note*: [a]AUDIT Zone I = 1; Zone II = 2; Zone III = 3; Zone 4 = IV.

TABLE 3 AUDIT zones and PEth marker categories: Number of patients.

	PEth 16:0/18:1	PEth 16:0/18:1	PEth 16:0/18:1	PEth 16:0/18:2	PEth 16:0/18:2	PEth 16:0/18:2	
	Low[e]	Moderate[f]	High[g]	Low[e]	Moderate[f]	High[g]	Total (*n*)
AUDIT Zone I[a]	236	27	3	225	31	10	266
AUDIT Zone II[b]	11	13	3	10	9	8	27
AUDIT Zone III[c]	1	1	3	1	0		5
AUDIT Zone IV[d]	0	0	3	0	0	3	3
AUDIT Zone III + IV[e]	1	1	6	1	0	7	8
Total	248	41	12	236	40	25	301

[a]AUDIT score 0–7 points; low risk drinking/abstinence.
[b]AUDIT| score 8–15 points; medium level of alcohol problems.
[c]AUDIT score 16–19 points; high level of alcohol problems.
[d]AUDIT score 20–40 points; high level of alcohol problems.
[e]PEth 16:0/18:1 < 20 μg/L | PEth 16:0/18:2 level < 10 μg/L; light drinking habits or abstinence.
[f]PEth 16:0/18:1 20–200 μg/L | PEth 16:0/18:2 10–67 μg/L; moderate alcohol consumption.
[g]PEth 16:0/18:1 > 200 μg/L | PEth 16:0/18:2 > 67 μg/L; excessive/high risk drinking.

TABLE 4 Linear regression analysis PEth 16:0/18:1|PEth 16:0/18:2, AUDIT, age, gender and TLFB two-week and TLFB 24 h.

	PEth 16:0/18:1[a]					PEth 16:0/18:2[b]				
	Unstandardized coefficients		Standardized coefficients			Unstandardized coefficients		Standardized coefficients		
	B	Std. Error	Beta	*t*	Sig	*B*	Std. Error	Beta	*t*	Sig
(Constant)	−35.518	33.102		−1.073	0.284	−41.897	29.299		−1.430	0.154
Age	0.030	0.415	0.003	0.072	0.943	0.066	0.367	0.008	0.180	0.857
Gender	8.191	13.263	0.026	0.618	0.537	11.127	11.740	0.040	0.948	0.344
AUDIT total score	9.543	2.091	0.273	4.563	0.000	9.214	1.851	0.297	4.978	0.000
TLFB 2 week	3.446	0.639	0.362	5.395	0.000	2.935	0.565	0.347	5.191	0.000
TLFB 24 h	24.714	6.879	0.187	3.593	0.000	21.226	6.088	0.182	3.486	0.001

[a]*R* square = 0.497.
[b]*R* square = 0.499.

on the AUDIT. Of the patients with moderate alcohol consumption according to the PEth 16:0/18:1|PEth 16:0/18:2 values, respectively 66% and 78% scored 'low risk drinking/abstinence' on the AUDIT. Most patients with low PEth 16:0/18:1|PEth 16:0/18:2 values (respectively 95% and 95%) showed 'low risk drinking/abstinence' (zone I) according to the AUDIT.

PEth values versus TLFB scores

Spearman correlation coefficient between PEth 16:0/18:1 and PEth 16:0/18:2 values and the TLFB two-week scores were high (PEth 16:0/18:1: 0.74, $p < 0.001$; PEth 16:0/18:2: 0.82, $p < 0.001$) and were comparable for males and females (PEth 16:0/18:1: 0.73 and 0.72, $p < 0.001$; PEth 16:0/18:2: 0.82 and 0.80, $p < 0.001$). Spearman correlation coefficient between the TLFB 24-h scores and PEth 16:0/18:1 and PEth 16:0/18:2 values were low (PEth 16:0/18:1: 0.46, $p < 0.001$; PEth 16:0/18:2: 0.49, $p < 0.001$) and were comparable for males and females (PEth 16:0/18:1: 0.48 and 0.39, $p < 0.001$; PEth 16:0/18:2: 0.51 and 0.41, $p < 0.001$).

The scores on the TLFB two-week questionnaire were significantly higher in patients who had a higher zone according to their AUDIT (Kruskal–Wallis Test; $p = 0.000$).

Multivariate linear regression analysis showed that the PEth 16:0/18:1 and PEth 16:0/18:2 values were significantly associated with the AUDIT score and the TLFB two-week and 24-h scores (Table 4). However, it should be noted that the dependent variables did not meet all the assumptions for the regression analyses.

DISCUSSION

The current study examined the correlation between two screening methods for hazardous alcohol use, the PEth marker, and the AUDIT, in a large sample of adult patients of the general ED population. This study showed a moderate correlation between the AUDIT scores and the PEth values. In the cases where the good correlation was absent, most patients had low AUDIT scores with high PEth values. Respectively, one in nine and one in six patients with low AUDIT scores had moderate or high PEth 16:0/18:1|PEth 16:0/18:2 values indicating moderate or excessive drinking. Also, in the high-risk category of patients with high PEth 16:0/18:1|PEth 16:0/18:2 values respectively 25% and 40% scored in the lowest AUDIT category. This is an alarming finding as this means that these patients had problematic alcohol use according to the PEth value but were not identified by the AUDIT.

This finding is in line with previous literature (Adong et al., 2019; Couture et al., 2016; Eyawo et al., 2018; Ferguson et al., 2020; Hahn, Emenyonu, et al., 2016; Irvin et al., 2020; Papas et al., 2016). For example, a study among the HIV positive patients showed that 36% scored positive on PEth while their AUDIT-C was negative (Hahn, Emenyonu, et al., 2016). Other studies among HIV-infected patients showed a similar discrepancy between self-reported alcohol use and the PEth value (Adong et al., 2019; Eyawo et al., 2018; Ferguson et al., 2020; Irvin et al., 2020; Papas et al., 2016). Couture et al. (2016) showed that 43% of the men and 5% of the women had a positive PEth while scoring negative on the AUDIT-C. Some studies showed higher agreement; Francis et al. (2015) showed that when compared to PEth, self-reported heavy alcohol intake has a sensitivity of 92–100% and a specificity of 64–85% among young people. Other studies in various populations have shown these good correlations as well (Jain et al., 2014; Kuteesa et al., 2019; Röhricht et al., 2020).

Previous studies among subgroups in the ED described results similar to the findings of the current study. Kip et al. (2008) showed that, among male patients presenting with thoracic/gastrointestinal complaints to the ED who had an AUDIT score below eight, 37% had a positive PEth indicating longer lasting intake of higher amounts of alcohol. In a subgroup of trauma patients in the ED, a significant correlation between the PEth values and the AUDIT-C scores was found, but 5% of the patients in this group reported abstinence although their PEth value indicated alcohol use (Gerbase et al., 2021). A possible explanation for these results is that participants might have underreported their drinking habits in the questionnaire, maybe due to social desirability or response bias or poor recalling (Adong et al., 2019; Couture et al., 2016; Hahn, Emenyonu, et al., 2016; Kip et al., 2008).

The finding that there are patients with problematic alcohol use according to the objective PEth value, who are not identified by the subjective AUDIT, is important because the different AUDIT zones have different guidelines for intervention. Based on the AUDIT guideline the intervention for zone 1 is 'alcohol education' while a high PEth value indicates excessive/high-risk drinking that would need much more intensive evaluation and treatment (World Health Organization, 2011). This shows the advantages of PEth as an additional screening method in the general ED population. This is also in line with literature where the advantages of this direct alcohol marker were shown in different populations (Couture et al., 2016; Francis et al., 2015; Gerbase et al., 2021; Hahn, Emenyonu, et al., 2016; Kip et al., 2008; Piano et al., 2015). Detection of this population at risk provides opportunities for possible future intervention strategies.

The high correlation between PEth 16:0/18:1 and PEth 16:0/18:2 versus the TLFB two-week scores found in this study was expected given that TLFB measures the amount of alcohol consumption in a period of time and since PEth markers are a metabolite of EtOH and can only be detected after alcohol use. It is therefore expected that higher reported intake results in higher PEth values (Viel et al., 2012). The lower correlation between the 24-h TLFB and PEth values can be explained by the fact that PEth is a marker that measures alcohol use over a longer period of time and alcohol intake could have taken place more than 24 h prior to presentation to the ED (Schröck et al., 2017; Wassenaar & Koch, 2015).

In the general Dutch population, 9% are heavy alcohol consumers and 8% meet the criteria of excessive drinking (Trimbos Insitute, 2019). The numbers in the current study appear somewhat higher than expected for 'medium level' and somewhat lower for 'high level' of alcohol problems according to the AUDIT; 9% of the patients had a medium level (zone II) and 3% of the patients had a high level (zone III + IV) of alcohol problems. The PEth 16:0/18:1 and PEth 16:0/18:2 values indicated moderate alcohol consumption in respectively 14% and 13% and these values indicated excessive/high-risk drinking in respectively 4% and 8% of the patients. The most likely explanation is that the current study examined a different population (the general Dutch population versus the ED population in an inner city hospital). Also, the different types of measurement and determination of terms could have influenced these numbers as well.

There are difficulties in determining a solid cut-off point for the values of PEth homologues for excessive alcohol consumption. This is well described in the literature and different cut-off points were found/used in previous studies in various populations (Afshar et al., 2017; Gerbase et al., 2021; Hahn, Anton, & Javors, 2016; Schröck et al., 2017; Simon, 2018; Stewart et al., 2014; Ulwelling & Smith, 2018; Viel et al., 2012). A comprehensive review from Viel et al. (2012) showed that, although the level of PEth cannot be directly translated into precise drinking level and concentrations vary significantly, the mean values and 95% CI of the PEth concentrations of heavy drinkers (DAI = daily alcohol intake >60 g) are well separated from the social drinkers (DAI man <40 g; woman <20). For PEth 16:0/18:1, the cut-off points used in this study were based on the review by Ulwelling and Smith (2018), who suggested these cut-off points based on consensus of multiple studies. Currently, there are no such consensus-based cut-off points available for PEth 16:0/18:2, therefore the cut-off points as described by Schröck et al. (2017) were used. The cut-off points of PEth 16:0/18:1 in the article of Schröck et al. (2017) compared to the review by Ulwelling and Smith (2018) shows that the cut-off points were lower in the

first-mentioned study, therefore it is possible that the cut-off points of PEth 16:0/18:2 could also be (somewhat) too low. As a result, the percentage of patients who were categorized as moderate and/or high risk according to the PEth 16:0/18:2 may have been overestimated.

Recently, Luginbühl et al. (2021) addressed the important matter of regioisomeric purity of reference materials when determining PEth. Ideally, reference substances from different distributors are used to check for regioisomeric purity to minimalize the possibility of impurity of the substances to the maximum. Unfortunately, during the analyses of the current study, only one distributor was available; it wasn't until 2021 that a second distributor became available. Therefore, different batch numbers were used to minimalize the chances of impurity of the reference substance.

A strength of the current study was the investigation of the general ED population instead of a subpopulation (Gerbase et al., 2021; Kip et al., 2008). This heterogeneous group regarding the reason of attendance, age, and gender strengthens the generalizability considering the use of screening instruments for problematic alcohol use in the general ED population. Further, both the AUDIT and TLFB were used to measure alcohol consumption patterns. The combination of both instruments gives the opportunity to evaluate both the total amount of alcohol use and also the average frequency and typical quantity of alcohol consumption (Schippers & Broekman, 2010; Sobell & Sobell, 1992). For future studies, it could also be interesting to compare PEth with the shorter-term objective marker EtG (van de Luitgaarden et al., 2019).

A possible limitation of the current study is that non-response bias could have been present since not all eligible patients that were approached to participate in this study gave informed consent (22% refused). Further, participation bias could be present since 21% of the patients were excluded because they were medically unable to give informed consent. This is a group where a routine questionnaire as screening method would be difficult to obtain and where determining a blood marker could be advantageous since the measurement is independent of the patient's wellbeing at that moment. Further research in these groups, e.g. with an opt-out procedure or deferred consent, is warranted to investigate problematic alcohol use and possible advantages of determining PEth in these patients.

CONCLUSIONS

The current study shows that AUDIT scores are moderately correlated with PEth values. In almost all cases where the good correlation was absent, the patients had high objective PEth values with low subjective AUDIT scores, meaning that problematic alcohol use was not detected by the AUDIT, but was very likely as measured by PEth. Therefore, this study concludes that PEth is a valuable addition to the AUDIT to identify patients with problematic alcohol use in the general ED population.

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CONFLICT OF INTEREST

None.

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