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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Increased admission serum estradiol level is correlated with high mortality in patients with severe acute pancreatitis

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Abstract
Background Sexual dimorphism in critical diseases has been documented. Severe acute pancreatitis is a disease with high mortality. We hypothesized that admission sex hormone levels may be used as an early predictor of outcome in these patients.
Methods A prospective cohort of patients with severe acute pancreatitis admitted to the intensive care unit for at least 48 h were enrolled ($n = 62$). Serum levels of estradiol, progesterone, and testosterone were determined on admission. The association of sex hormone levels and various disease severity scoring systems with patient outcome was analyzed.
Results There was no difference in overall mortality between the sexes. However, estradiol was significantly elevated in nonsurvivors (39 vs. 206 pg/mL, $p < 0.001$). The estradiol level was the best single-variable predictor of mortality (area under the curve 0.97), followed by the sequential organ failure assessment score, the multiple organ dysfunction score, and the Acute Physiology and Chronic Health Care Evaluation II (APACHE II) score. A serum estradiol level of 102 pg/mL was both sensitive and specific to predict mortality. There were no differences between survivors and non-survivors in terms of age, body mass index, or progesterone and testosterone levels.
Conclusions Admission serum estradiol level is a good marker of disease severity and predictor of death in patients with severe acute pancreatitis.

Keywords Acute pancreatitis · Estradiol · Mortality

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Introduction

The incidence of acute pancreatitis has increased during the past 2 decades [1, 2]. About 20 % of these patients have a progressive disease which eventually develops into severe acute pancreatitis (SAP) along with various serious complications. Multiple organ dysfunction is commonly seen in these patients, with an overall mortality rate of approximately 30–40 % [1, 3, 4]. Thus, early identification of patients likely or unlikely to have a fatal outcome following SAP may assist physicians to start appropriate therapy.

Although sexual dimorphism in trauma-hemorrhagic shock and sepsis is well documented in animal and clinical studies, the role of sex hormones in patient outcome is still not clear [5]. Among all the sex hormones, estrogen has been shown to have salutary effects on restoring immune function and suppressing inflammatory responses following trauma-hemorrhage and sepsis [6]. In contrast, however, May et al. [7] demonstrated that an elevated serum level of endogenous estrogen was associated with poor outcome in critically ill trauma and surgical patients. They analyzed serum estradiol levels in these patients within 48 h of admission and found that there was a three-fold increase in the mortality rate for those who had the highest versus the lowest estradiol quartiles (29 vs. 8 %, $p < 0.001$). In another study, Dossett et al. [8] reported that the serum level of estradiol was a marker of injury severity and a predictor of death in the critically injured patient regardless of gender.

Early identification of these high-risk patients is important as there is a chance to improve the survival of these patients by providing aggressive treatments in a timely fashion [6–8]. The aim of this study was to examine whether sex hormone levels determined at the time of intensive care unit (ICU) admission could be an early marker of the disease severity and a predictor of death in patients with SAP.

Patients and methods

Study population

Sixty-two consecutive patients with SAP who were admitted to and stayed in the surgical ICU for at least 48 h were enrolled in this prospective study. The diagnosis of SAP was made based on the criteria proposed by the International Atlanta Symposium on Acute Pancreatitis in 1992 [9–11]: (1) organ failure with 1 or more of the following: shock (systolic blood pressure <90 mmHg), pulmonary insufficiency (partial arterial pressure of oxygen ≤60 mmHg), renal failure (serum creatinine level >2 mg/dL after rehydration), or gastrointestinal tract bleeding (>500 mL in 24 h); (2) local complications such as necrosis, pseudocyst, or abscess; (3) at least 3 of Ranson's criteria; or (4) at least 8 of the Acute Physiology and Chronic Health Care Evaluation II (APACHE II) criteria. Pregnant women and patients younger than 18 years old were excluded. All the patients received standardized treatment according to a treatment guideline for acute pancreatitis published in 2006 [11].

Data collection

Age, gender, body mass index (BMI), time interval between the onset of symptoms and ICU admission, in-hospital mortality, etiology of SAP, presence of infected pancreatic necrosis (IPN), and types of treatments were recorded. The serum procalcitonin (PCT) level [12, 13], the 48-h Ranson score [14], the APACHE II score, the multiple organ dysfunction score (MODS) [15], the sequential organ failure assessment (SOFA) score [16], and the computed-tomography severity index (CTSI) [17] were also collected on ICU admission for evaluation of severity of the disease.

Sex hormone assays

One 4.5-mL blood sample was collected within the first 4 h after ICU admission for analysis of hormone levels. Serum levels of 17β-estradiol (E2), progesterone, and testosterone were determined using commercially available immunoassays (Beckman Coulter Acess® Reagent; Beckman Coulter, Brea, CA, USA) at the Clinical Laboratory Department of China Medical University Hospital. The results for steroid hormone levels could be obtained within 2 h.

Statistical analysis

The Shapiro–Wilk test was used to test the distributions of all continuous variables for normality. Normally distributed continuous variables were summarized by reporting their mean and standard deviation (SD) and were compared by using independent *t*-tests. Continuous variables that were not normally distributed were presented as medians and interquartile ranges (IQRs) and were compared by using Wilcoxon's rank sum test. Differences in proportions were compared using Fisher's exact test or the χ^2 test. A logistic regression model was used to investigate the relationships between clinical variables and mortality. The area under the receiver operating characteristic curve (AUROC) was calculated to compare the effectiveness of mortality prediction of each logistic regression model. A test was considered to be more accurate in the prediction of mortality if its AUROC approached 1.0; while it was of little diagnostic value if its AUROC approached 0.5. SAS 9.1 (SAS Institute, Cary, NC, USA) was used for the entire analysis. Tests for statistical significance were two-sided with the level of significance set at 0.05. The predictive power of indicators was demonstrated by calculating their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) by using the optimal cutoff.

This study was approved by the Institutional Review Board of China Medical University Hospital (DMR99-IRB-232). Families were asked for their consent during the critical illness phase, and, when possible, patients provided informed consent after their critical illness resolved. All data and all patient information were de-identified before analysis and reporting.

Results

A total of 62 patients with SAP were included in this study. The overall in-hospital mortality rate was 24.1 % (15 deaths). The demographics, clinical characteristics, disease severity scores, and hormone levels by sex are shown in Table 1. There were 49 male patients (79 %) and 13 female patients (21 %). The male patients were significantly younger than the female patients (47 vs. 68 years, $p = 0.01$). The overall mortality rates for men and women were not significantly different (22.4 vs. 30.7 %, $p = 0.716$). The etiology of SAP was alcoholic in 32 (52 %), biliary in 19 (30 %), and hypertriglyceridemia in 11 (18 %) patients. Regarding the sex hormones, the serum level of testosterone was significantly higher in the male patients, but no differences between the sexes were demonstrated in E2 or progesterone levels. Also, no differences between the sexes were observed in the APACHE II score, Ranson score, CTSI, MODS, SOFA score, and Child–Pugh score; or in PCT levels and the incidence of IPN.

Table 1 Demographics and clinical characteristics by sex

	Male ($n = 49$)	Female ($n = 13$)	p value
Age (years)[a]	47.0 (36.0–57.0)	68.0 (55.0–78.0)	0.010
Deaths [n (%)][b]	11 (22.4 %)	4 (30.7 %)	0.716
BMI[a]	26.1 (23.4–29.5)	22.6 (21.8–26.2)	0.100
APACHE II[a]	17.0 (14.0–24.0)	22.0 (15.0–28.0)	0.136
Ranson score[a]	5.0 (4.0–6.0)	6.0 (4.0–7.0)	0.450
CTSI[a]	6.0 (4.0–7.0)	6.0 (4.0–8.0)	0.634
MODS[a]	6.0 (3.0–10.0)	8.0 (6.0–12.0)	0.241
SOFA score[a]	6.0 (3.0–9.0)	7.0 (4.0–10.0)	0.386
PCT (ng/mL)[a]	3.0 (1.0–8.0)	12.0 (3.0–23.6)	0.031
Estradiol (pg/mL)[a]	50.0 (31.0–102.0)	53.0 (37.0–206.0)	0.473
Progesterone (ng/mL)[a]	1.1 (0.6–1.8)	1.1 (0.4–2.1)	0.815
Testosterone (ng/mL)[a]	0.6 (0.4–1.1)	0.2 (0.2–0.3)	0.001
IPN [n (%)][b]	12 (24.49 %)	5 (38.46 %)	0.319
Child–Pugh score[a]	7 (6–7)	7 (7–8)	0.216
Etiology of SAP [n (%)][b]			0.037
Biliary[b]	11 (22.45 %)	8 (61.54 %)	0.015
Alcoholic[c]	28 (57.14 %)	4 (30.77 %)	0.091
TG >1000 mg/dl[b]	10 (20.41 %)	1 (7.69 %)	0.431

BMI body mass index, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *CTSI* computed-tomography severity index, *MODS* Multiple Organ Dysfunction score, *SOFA* Sequential Organ Failure Assessment, *PCT* procalcitonin, *IPN* infected pancreatic necrosis, *TG* triglyceridemia, *SAP* severe acute pancreatitis

[a] Median (interquartile range), compared by Wilcoxon's rank-sum test

[b] N (proportion), compared by Fisher's exact test

[c] N (proportion), compared by the χ^2test. A p value of <0.05 was considered statistically significant

The demographic characteristics, disease severity scoring, and clinical presentations of all 62 patients are shown by outcome in Table 2. As expected, traditional predictors of disease severity and mortality such as the APACHE II score, Ranson score, CTSI, MODS, and SOFA score; PCT; and the incidence of IPN were significantly higher in the non-survivor group. Most of the survivors were treated non-operatively, while the majority of the non-survivors required either percutaneous drainage or laparotomy. However, the time intervals between the onset of symptoms and ICU admission were similar in the survivors and non-survivors (median 2.1 vs. 2.3 days, $p = 0{,}628$). Also, age, gender, BMI, and etiology of pancreatitis were not associated with mortality. Moreover, the median Child–Pugh scores for the severity of chronic liver disease were also similar in the survivors and non-survivors. Of all the sex hormones tested, E2 was the only hormone that was significantly higher in non-survivors ($p < 0.001$). The median serum E2 level in non-survivors was 5.3 times higher than that in survivors [206 pg/mL (IQR 148–241) vs. 39 pg/mL (IQR 27–59), $p < 0.001$]. In contrast, there were no significant differences in the serum levels of testosterone or progesterone between survivors and non-survivors.

Given the highly significant association between E2 levels and mortality, additional analyses of this relationship were done. Median E2 levels for survivors and non-survivors in both men and women, in young and old patients, and in patients with above and below the mean APACHE II score, are presented in Table 3. In all subgroups, values of median E2 levels for non-survivors were roughly two to five times higher than those of survivors, and all differences reached statistical significance.

We then tested the individual and the combined values of the APACHE II score, Ranson score, CTSI, MODS, and SOFA score; IPN; and the serum levels of PCT and E2 by logistic regression modeling (as determined by the AUROC) for mortality prediction. The results of risk analysis for mortality according to the selected models are shown in Table 4. In the single-variable model, E2 levels were the best single-variable predictor of mortality (area under the curve 0.97), followed by the SOFA score (area under the curve 0.90), MODS (area under the curve 0.88), and APACHE II (area under the curve 0.87). The AUROCs (0.97) of the E2 level + Ranson score + APACHE II score and SOFA score + IPN were the highest. However, because age, white cell count (WBC), hemoglobin, and partial arterial pressure of oxygen (PaO_2) were overlapping parameters in the Ranson score and APACHE II score, the best multivariate regression model predictor of overall mortality was the SOFA score plus IPN (area under the curve 0.97).

Table 2 Demographics and clinical characteristics of the survivors and non-survivors

	Survivors ($n = 47$)	Non-survivors ($n = 15$)	p value
Time interval between onset of symptoms and admission to ICU[a]	2.1 (1.3)	2.3 (1.5)	0.628
Age (years)[a]	51.6 (18.7)	55.1 (18.1)	0.523
Male [n (%)][b]	38 (80.9 %)	11 (73.3 %)	0.716
BMI[a]	26.1 (4.6)	26.9 (4.6)	0.524
APACHE II[c]	16.0 (14.0–20.0)	28.0 (24.0–32.0)	<0.001
Ranson score[c]	5.0 (3.0–6.0)	7.0 (6.0–8.0)	<0.001
CTSI[c]	6.0 (4.0–6.0)	9.0 (8.0–10.0)	<0.001
MODS[c]	5.0 (2.0–8.0)	11.0 (10.0–15.0)	<0.001
SOFA score[c]	5.0 (3.0–7.0)	11.0 (9.0–16.0)	<0.001
PCT (ng/mL)[c]	2.0 (1.0–4.5)	12.0 (8.8–25.6)	<0.001
Estradiol (pg/mL)[c]	39.0 (27.0–59.0)	206.0 (148.0–241.0)	<0.001
Progesterone (ng/mL)[c]	1.1 (0.5–1.8)	2.0 (0.7–4.5)	0.093
Testosterone (ng/mL)[c]	0.5 (0.2–1.1)	0.5 (0.3–0.6)	0.888
IPN [n (%)][b]	6 (12.77 %)	11 (73.33 %)	<0.001
Child–Pugh score[c]	7 (6–7)	7 (7–8)	0.098
Etiology of SAP [n (%)][b]			0.317
Biliary[b]	12 (25.53 %)	7 (46.67 %)	0.197
Alcoholic[d]	26 (55.32 %)	6 (40 %)	0.301
TG >1000 mg/dL[b]	9 (19.15 %)	2 (13.33 %)	1.000
Treatment [n (%)][b]			<0.001
Conservative	41 (87.2 %)	3 (20 %)	
Percutaneous drainage	4 (8.5 %)	4 (26.7 %)	
Laparotomy	2 (4.3 %)	8 (53.3 %)	

ICU intensive care unit, *BMI* body mass index, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *CTSI* computed-tomography severity index, *MODS* Multiple Organ Dysfunction score, *SOFA* Sequential Organ Failure Assessment, *PCT* procalcitonin, *IPN* infected pancreatic necrosis, *TG* triglyceridemia, *SAP* severe acute pancreatitis

[a] Median (interquartile range), compared by Wilcoxon's rank-sum test

[b] N (proportion), compared by Fisher's exact test

[c] N (proportion), compared by the χ^2test. A p value of <0.05 was considered statistically significant

The optimal cutoff value; the sensitivity, specificity, PPV, and NPV; and the overall accuracy of the eight parameters–the APACHE II score, Ranson score, CTSI, MODS, SOFA score, IPN, and the serum levels of PCT and E2–to predict the mortality of SAP are shown in Table 5. Of these eight parameters, E2 had the greatest overall accuracy. A serum E2 level of 102 pg/mL or more had the highest sensitivity (93 %) and specificity (91 %) to predict mortality for patients with SAP. The PPV and NPV for E2 2 were 77 and 97 %, respectively. The optimum cutoff levels of the APACHE II score, Ranson score, CTSI, PCT, MODS, and SOFA score were ≥24, ≥7, ≥8, ≥6.4 ng/mL, ≥9, and ≥9, respectively.

Moreover, there was a linear relationship between the six scoring systems and serum E2 levels which indicated that an elevated serum E2 level was associated with increased disease severity (Table 6).

Table 3 Estradiol levels by outcome stratified by different variables

	n	Survivors	n	Non-survivors	p value
Women	9	37.0 (29–53)	4	208.5 (169–312)	0.025
Men	38	40.5 (27–59)	11	185.0 (148–241)	<0.001
Age <52 years	25	37.0 (23–50)	7	207.0 (168–246)	<0.001
Age ≥52 years	22	45.5 (33–73)	8	177.0 (140–219.5)	0.001
APACHE II <24	41	39.0 (24–52)	3	132.0 (55–241)	0.015
APACHE II ≥24	6	83.5 (33–124)	12	206.5 (158–237)	0.017

APACHE II Acute Physiology and Chronic Health Evaluation II

Data are shown as medians (interquartile ranges), compared by Wilcoxon's rank-sum test. A p value of <0.05 was considered statistically significant

Table 4 Area under the receiver operating characteristic curve (ROC) for selected individual variables by multivariate logistic regression models

Variable	AUROC[a]
APACHE II	0.87
Ranson score	0.82
E2	0.97
CTSI	0.82
MODS	0.88
SOFA score	0.90
PCT	0.82
IPN	0.80
APACHE II + Ranson score + E2	0.97
MODS + IPN	0.95
SOFA score + IPN	0.97

APACHE II Acute Physiology and Chronic Health Evaluation II, *E2* estradiol, *CTSI* computed-tomography severity index, *MODS* Multiple Organ Dysfunction Score, *SOFA* Sequential Organ Failure Assessment, *PCT* procalcitonin, *IPN* infected pancreatic necrosis

[a] Area under the receiver operating characteristic (ROC) curve

Table 5 Capability of APACHE II score, Ranson score, CTSI, E2, PCT, MODS, SOFA score, and IPN to predict mortality in severe acute pancreatitis

Diagnostic tools	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
APACHE II ≥24	80	87	66	93	85
Ranson score ≥7	66	89	66	89	84
CTSI ≥8	80	91	75	93	88
E2 ≥102 pg/mL	93	91	77	97	92
PCT ≥6.4 ng/mL	86	76	54	94	79
MODS ≥9	93	78	58	97	82
SOFA score ≥9	86	87	68	95	87
Presence of IPN	73	87	64	91	84

APACHE II Acute Physiology and Chronic Health Evaluation II, *CTSI* computed-tomography severity index, *E2* estradiol, *PCT* procalcitonin, *MODS* Multiple Organ Dysfunction Score, *SOFA* Sequential Organ Failure Assessment, *IPN* infected pancreatic necrosis

Table 6 Correlation coefficient analysis of various markers and scoring systems

	APACHE II score	Ranson score	E2	CTSI	MODS	SOFA score	PCT
APACHE II	1.00	0.76***	0.68***	0.46***	0.77***	0.71***	0.46***
Ranson score		1.00	0.67***	0.35**	0.58***	0.56***	0.40**
E2			1.00	0.43***	0.63***	0.67***	0.62***
CTSI				1.00	0.51***	0.53***	0.39**
MODS					1.00	0.93***	0.48***
SOFA score						1.00	0.48***
PCT							1.00

APACHE II Acute Physiology and Chronic Health Evaluation II, *CTSI* computed-tomography severity index, *E2* estradiol, *PCT* procalcitonin, *MODS* Multiple Organ Dysfunction Score, *SOFA* Sequential Organ Failure Assessment

Values are Spearman correlation coefficients. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Discussion

There is evidence suggesting that high levels of serum E2 are associated with increased mortality in critically ill trauma patients and in patients with severe infection [7, 8, 18, 19]. Angstwurm et al. [20] found that elevated serum E2 was correlated with increased mortality in both elderly male and female patients with infections, indicating that the E2 level rather than gender was associated with prognosis in septic patients. However, the correlations between serum E2 levels and outcome in patients with SAP remained unknown.

The pathophysiology of SAP is the extensive destruction of pancreatic parenchyma, which rapidly leads to an overwhelming systemic inflammatory response and multiple organ failure [21, 22]; that is, SAP has a mechanism similar to that of other critical illnesses such as sepsis and trauma-hemorrhage. Although aromatase activity in SAP has not been investigated, there is evidence showing that aromatase activity was upregulated following an acute illness. Spratt et al. [23] reported that, in patients with acute illness, the expression of the aromatase *P450* gene was increased, resulting in the enhanced aromatization of androgen and increased peripheral biosynthesis of estrogen. In a murine model of trauma-hemorrhagic shock, Samy et al. [24] showed that the estrogen synthesis and aromatase activities of lymphocytes were significantly increased following trauma-hemorrhage compared with findings in sham-operated animals, while the expression of estrogen receptor (ER)-β was significantly decreased following the trauma-hemorrhage. In contrast, in ovariectomized animals, the synthesis of E2 and the activity of aromatase were not increased following trauma-hemorrhage, and the expression of ER-β was not decreased [24]. Their results suggested a strong association between aromatase activity and ER expression. Using the same animal

model, Schneider et al. [25] demonstrated that the administration of an aromatase inhibitor after trauma-hemorrhage could restore the suppressed expression of ER-β and the depressed immune functions of splenic lymphocytes. Because the effects of E2 as well as the systemic inflammatory responses following acute illnesses are usually neither cell-type- nor insult-specific [26, 27], it is possible that the increased E2 we observed in SAP was also due to upregulated aromatase activity which led to the downregulation of ER expression.

One may argue that while elevated endogenous E2 levels were associated with poor outcome in the present study, conversely there are a number of investigations showing conflicting results, i.e., that the administration of estrogen after trauma-hemorrhage significantly reduced mortality [28–30]. The action of estrogen relies on ERs. It is now understood that the physiological effect of estrogen is mediated by either intracellular ERs (genomic effect, slow response) or by cell-surface receptors such as GPR30 (non-genomic effect, rapid response) [29, 30]. As the administration of E2 has been shown to rapidly restore cardiopulmonary, hepatic, and immune functions following critical illness, it is likely that the actions of acute pharmacologic doses of estrogen are largely mediated via the non-genomic pathway [26, 31, 32]. Because conventional intracellular ERs are downregulated following critical illness, the genomic effects of estrogen mediated by ERs are unlikely to exert a rapid response [30]. On the other hand, the role of endogenous E2 during critical illness is less clear. Although there is some cellular evidence suggesting that endogenous estrogen might elicit proinflammatory but not anti-inflammatory responses via ER signaling [33], relevant data regarding the effect of endogenous estrogen are inconsistent and have most often been obtained from observational studies such as those examining differences between males and premenopausal females, or differences between normal and ovariectomized animals [5, 34–37]. Taken together, the above evidence indicates that E2 administration has a clearly shown anti-inflammatory, immune-modulating effect in many diseases; in contrast, it is still not clear whether endogenous E2 is a mediator of the inflammatory process or is whether it is simply a marker of disease [8, 18, 36, 38]. Nonetheless, our data, although preliminary, suggest that estrogen/ER modulation represents a potential therapy to improve outcomes for patients with SAP.

Early diagnosis of SAP is important because it might lead to a better prognosis by prompting aggressive treatments such the continuous regional arterial infusion of protease inhibitors and antibiotics [39–41]. Some scoring systems including the Ranson score [42, 43], APACHE II score, MODS, SOFA score, and CTSI have been used to help in identifying patients with SAP who are at risk of an adverse outcome [15–17]. However, the utility of these scoring systems to predict outcomes in SAP patients is still inconclusive, as large variations exist among the different scoring systems and different studies [44–46]. Following the discovery of the significant associations between estrogen/ERs and their influence on organ systems during critical conditions, it will be interesting to see if estrogen levels can also be used to predict patient outcome. Dossett et al. [18] showed that a serum E2 cutoff point value of 50 pg/mL had 48 % sensitivity and 80 % specificity in predicting mortality in critically ill patients, and its overall accuracy was 76 %. Our results showed that, measured at roughly the same time point as that used by Dossett et al. [18] (2 days after the onset of disease), the serum E2 levels in the non-survivors had been significantly elevated at the time of ICU admission and were 5.3 times higher than those of the survivors [206 pg/mL (IQR 148–241) vs. 39 pg/mL (IQR 27–59), $p < 0.001$]. In addition, the median E2 levels in the non-survivors were also roughly 2–5 times higher than those in the survivors in each sex, age, or APACHE II stratified subgroup. E2 was also a more powerful independent predictor (AUROC 0.97) than the SOFA score (AUROC 0.90), MODS (AUROC 0.88), and the APACHE II score (AUROC 0.87) for the outcome in SAP patients. By applying the ROC curve model we found that a sensitivity of 93 % and a specificity of 91 % could be achieved for the prediction of mortality if a serum E2 level of 102 pg/mL was chosen as the cutoff point. Furthermore, although the AUROC of the SOFA score plus IPN was as high as that of E2 in predicting mortality in SAP patients (Table 4), it should be noted that serum E2 levels could be obtained within 2 h of ICU admission while it would take several days to confirm the presence of IPN. Hence, serum E2 levels were a better indicator for the early prediction of mortality in SAP patients. Moreover, the strong correlation coefficients between E2 and the other six scoring systems we used also proved the reliability of serum E2 levels as an indicator of disease severity.

It is well known that serum E2 levels are increased in patients with liver cirrhosis [47]. Therefore, one may speculate that the increased E2 levels in non-survivors in our study resulted from their higher incidence of severe cirrhosis compared to that in the survivors. However, we found that the Child–Pugh scores in the survivors and non-survivors were not significantly different, and, in addition, the serum testosterone levels were not lower in non-survivors (although lower serum testosterone levels are often observed in cirrhotic patients) [48]. These results suggested that cirrhosis was less likely to be a contributing factor to mortality in our SAP patients and that it was also less likely to be the primary reason for the elevated serum E2 levels in the non-survivors.

Sex has been considered to be a determinant of immunologic variability after severe traumatic and surgical stress that accounts for differences in outcomes [6, 36, 49]. Other studies found that mortality was not dependent on gender but was correlated with elevated serum estrogen levels in both genders [8, 18]. Our results showed that gender was not a good predictor of mortality for SAP patients ($p = 0.716$). Moreover, there were no differences between survivors and non-survivors in terms of testosterone and progesterone levels. E2 was the only sex hormone that predicted mortality in our SAP patients ($p < 0.001$).

Old age is no doubt an unfavorable factor and is associated with higher mortality in most diseases compared with mortality in younger patients. However, our single-variable analysis showed that age was not a significantly independent predictor of mortality in SAP patients ($p = 0.523$). A possible explanation for this finding was that SAP mostly occurred in middle-aged patients and therefore there were no statistically significant differences in age between the survivors and non-survivors of the disease.

A major limitation of the present study is that there were no data on serial changes in E2 levels following ICU admission. It is not known whether a trend of progressively increasing E2 levels during the course of SAP predicts mortality, or whether a trend of E2 levels returning to baseline indicates full recovery. In a prospective cohort study of 1,408 critically ill patients whose E2 levels were measured on ICU admission as well as 2–5 days after admission, Kauffmann et al. [38] demonstrated that although the admission E2 level alone was a strong predictor of mortality, the power of prediction was even greater if the trend of the change of E2 levels was included along with admission E2 levels. In this regard a similar study should be applied in SAP patients to verify the strength of the E2 level as a marker of the prognosis in these patients. However, to identify a patient with high risk of mortality early in the course of a disease, a biomarker is less useful if it has to be measured serially to show a trend for prognosis prediction. This is because until that time the disease may have already become too advanced to start an effective treatment. From this point of view, E2 seems to be a good marker because its value can be obtained early on admission and a single value alone is powerful enough to identify high-risk SAP patients.

Conclusion

Serum E2 correlates with mortality in SAP patients and is a potential marker of severity and a predictor of death in these patients. A serum E2 level of 102 pg/mL could be used as a good cutoff point value for the early identification of patients with increased risk of mortality. Although our data were based on a limited number of patients and the results were preliminary, the diagnostic and therapeutic potential of these findings warrant further investigation.

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