Development of disturbance of consciousness is associated with increased severity in acute pancreatitis

Roland Hágendorn [a, b], Áron Vincze [a], Ferenc Izbéki [c], László Gajdán [c], Szilárd Gódi [a], Anita Illés [a], Patrícia Sarlós [a], Nelli Farkas [d, e], Bálint Erőss [d], Veronika Lillik [d], Dóra Illés [f], Péter Varjú [d], Katalin Márta [d], Imola Török [g], Mária Papp [h], Zsuzsanna Vitális [h], Barnabás Bod [i], József Hamvas [j], Zoltán Szepes [f], Tamás Takács [f], László Czakó [f], Zsolt Márton [k], Andrea Szentesi [d, f], Andrea Párniczky [b, d, l], Péter Hegyi [d, m, n], Alexandra Mikó [a, b, d, *]

[a] Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[b] School of Clinical Medicine, University of Szeged, Szeged, Hungary
[c] Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary
[d] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Hungary
[e] Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary
[f] 1st Department of Medicine, University of Szeged, Szeged, Hungary
[g] County Emergency Clinical Hospital Târgu Mures, George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș, Romania
[h] Department of Internal Medicine, Division of Gastroenterology, University of Debrecen, Debrecen, Hungary
[i] Bugyi István Hospital, Szentes, Hungary
[j] Bajcsy-Zsilinszky Hospital, Budapest, Hungary
[k] Intensive Care Unit, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[l] Heim Pál National Institute for Pediatrics, Budapest, Hungary
[m] Division of Translational Medicine, First Department of Medicine, Medical School, University of Pécs, Hungary
[n] Hungarian Academy of Sciences, University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group, Szeged, Hungary

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ABSTRACT

Background: Disturbance of consciousness (DOC) may develop in acute pancreatitis (AP). In clinical practice, it is known that DOC may worsen the patient's condition, but we have no exact data on how DOC affects the outcome of AP.
Methods: From the Hungarian Pancreatic Study Groups' AP registry, 1220 prospectively collected cases were analyzed, which contained exact data on DOC, included patients with confusion, delirium, convulsion, and alcohol withdrawal, answering a post hoc defined research question. Patients were separated to Non-DOC and DOC, whereas DOC was further divided into non-alcohol related DOC (Non-ALC DOC) and ALC DOC groups. For statistical analysis, independent sample *t*-test, Mann-Whitney, Chi-squared, or Fisher exact test were used.
Results: From the 1220 patients, 47 (3.9%) developed DOC, 23 (48.9%) cases were ALC DOC vs. 24 (51.1%) Non-ALC DOC. Analysis between the DOC and Non-DOC groups showed a higher incidence of severe AP (19.2% vs. 5.3%, p < 0.001), higher mortality (14.9% vs. 1.7%, p < 0.001), and a longer length of hospitalization (LOH) (Me = 11; IQR: 8—17 days vs. Me = 9; IQR: 6—13 days, p = 0.049) respectively. Patients with ALC DOC developed more frequently moderate AP vs. Non-ALC DOC (43.5% vs. 12.5%), while the incidence of severe AP was higher in Non-ALC vs. ALC DOC group (33.3% vs. 4.4%) (p < 0.001). LOH showed a tendency to be longer in Non-ALC DOC compared to ALC DOC, respectively (Me:13; IQR:7—20 days vs. Me:9.5; IQR:8—15.5 days, p = 0.119).

* Corresponding author. Institute for Translational Medicine, Medical School, University of Pécs, Szigeti Street 12., II. floor, Pécs, 7624, Hungary.
E-mail addresses: miko.szandi@gmail.com, alexandra.miko@aok.pte.hu (A. Mikó).

Conclusion: DOC during AP is associated with a higher rate of moderate and severe AP and increases the risk of mortality.

Introduction

Acute pancreatitis (AP) is a sterile inflammation of the pancreas, leading to hospitalization, which is one of the most common among gastrointestinal diseases [1]. Based on the revised Atlanta classification, the severity of AP may be classified as mild, moderate, or severe [2], the presence of local complication, and organ failure differentiates between the grades of severity. The prognosis of the severe form is poor; it evolves in 8.8% in AP, and the mortality may reach 28% in the severe cases [3]. In case of moderate AP, organ failure develops and resolves within 48 h, while in severe forms, it persists longer [2]. The modified Marshall scoring system reports that six dysfunctional organ systems strongly correlates with mortality and intensive care unit (ICU) admission [4]. From these, renal-cardiovascular and respiratory failures are mentioned and discussed the most frequently, while the neurologic complications and monitoring of the Glasgow Coma Scale (GCS) are not well studied in the relevance of AP.

There are several risk factors worsening severity and mortality, but there is little knowledge of the factors that have an effect on the outcome of the disease [5–9]. In clinical practice, patients with AP might present with several neurological symptoms, including 1) alcohol withdrawal syndrome, 2) confusion or delirium characterized by a disturbance of consciousness (DOC), 3) with reduced ability to focus, sustain, or shift attention with different etiological factors. In the pathophysiological background, during chronic alcohol exposure, N-methyl-D-aspartate (NMDA) receptors are upregulated, and gamma-aminobutyric acid type-A (GABAA) receptors are downregulated, leading to tolerance. Alcohol withdrawal causes the opposite effect as enhanced NMDA receptor function, reduced GABAergic transmission, and dysregulation of the dopaminergic system, leading to signs of withdrawal syndrome like tremors, diaphoresis, tachycardia, anxiety, and seizures [10]. Delirium tremens is the most severe form of alcohol withdrawal. It is characterized by sudden and severe mental or nervous system changes. Leading signs are altered mental status (global confusion) and sympathetic overdrive (autonomic hyperactivity), which can progress to cardiovascular collapse. It is a medical emergency with a high mortality rate, making early recognition and treatment essential. The prevalence of delirium in the elderly population is between 29 and 64% [11], and its financial burden is extreme for the health care system [12] independently form the various etiological factors.

The few available reports about pancreatic encephalopathy reported different hypotheses about the underlying mechanisms; one even concluded that it is difficult to differentiate it from Wernicke encephalopathy [13]. Until now, no study focused on the influencing role of DOC on the outcome of AP. We aimed to determine its effect by a cohort analysis.

Methods

The Hungarian Pancreatic Study Group (HPSG) established a prospective international registry containing AP patients' data. All participants signed the written consent form. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU). For this HPSG cohort study data of 1220 patients were used, since they contained data about the level of consciousness during hospitalization. This cohort overlaps with the cohorts discussed in our previous articles [3,8,9], but data and results of the analysis on DOC are only published in this report. Data were collected between January 2013 and January 2017. Based on the presence of DOC, patients were sorted into DOC and Non-DOC groups. The DOC group was further divided into alcohol-related DOC (ALC DOC) and non-alcohol related DOC (Non-ALC DOC).

Definition and data collection

DOC was diagnosed if the patient had confusion, disorientation, memory deficit, hyper- or hypoactivity, or symptoms of alcohol withdrawal such as anxiety, shaky hands, headache, insomnia or sweating, or epileptic seizure; or signs of delirium. The information of DOC was collected from the prospectively collected database of the HPSG registry and the patients' documentation, answering a post hoc defined research question. In severe cases, the documentation also included psychiatric consultation. Supplementary Table 2 contains the data of DOC of the 47 analyzed patients: time of onset, number of episodes, duration of DOC, description of symptoms, and applied therapy.

Statistical analysis

Descriptive statistical tools were used to characterize our cohort. To examine differences between the groups, in case of age, we used an independent sample *t*-test, whereas the length of hospitalization (LOH) with the Mann-Whitney test were analyzed. To analyze the connection between severity, mortality, and DOC, and between the time of onset of DOC and severity, the Chi-squared test or Fisher exact test was performed. All statistical analyses were done using SPSS Ver. 24 Software (IBM Corporation Armonk, New York). The significance level was set at 0.05.

Results

General characteristics of the entire cohort

A total of 1220 cases from 20 centers were analyzed. The list of centers is shown in Supplementary Table 1. Data were complete for age, gender, etiology of pancreatitis, LOH, the severity of acute pancreatitis, and mortality. Our registry included data about alcohol consumption in 99.6% (Table 1). The basic characteristics of the analyzed population are shown in Fig. 1. More than half of our patients were male (n = 683), and 46% were female (n = 537). The most common etiological factor was biliary pancreatitis (38.4%, n = 469), followed by idiopathic (19.2%, n = 234), and alcohol-induced pancreatitis (15.2%, n = 186). In the case of acute alcoholic pancreatitis, male dominance can be seen (male 87%, n = 162; female 13%, n = 24). In some cases, we found combined etiology (11.9%). In our study, 67.5% of the cases were mild. Moderate pancreatitis was observed in 26.7% of cases and severe inflammation in 5.8% of the cases. The LOH was almost three times more (23.5 days ± 2.5) in case of severe acute pancreatitis than in mild ones (8.6 days ± 0.17). In moderate cases, the average LOH was

Table 1
Quality characteristics of the Hungarian Pancreatic Study Group registry for the 1220 patients with acute pancreatitis.

Epidemiology, etiology, outcome	OVERALL	UPLOADED DATA	%
Age	1220	1220	100
Gender	1220	1220	100
Etiology	1220	1220	100
Alcohol consumption	1220	1216	99.6
Length of hospitalization	1220	1220	100
Severity of AP	1220	1220	100
Mortality	1220	1220	100
Average uploaded data			99.9

18 ± 0.7 days. The total mortality rate was 2.4%. In severe cases, the mortality reached 29.9%, in mild cases, 0.2% only, and in moderate cases, 2.2%. (Fig. 1A–F).

Demographic characteristics in DOC vs. Non-DOC groups

From the 1220 patients of the HPSG registry, 47 patients (3.9%) developed DOC (Fig. 2A). Based on the type of DOC, delirium (n = 18), confusion (n = 16), alcohol withdrawal syndrome (n = 9), and convulsion (n = 3) groups were identified. According to the etiology of DOC, in our cohort, alcohol (n = 23), older age (n = 9), and sepsis (n = 6) caused the most cases of DOC. However, ischemia (n = 3) hypoglycemia (n = 1) and electrolyte imbalance (n = 1) also caused DOC. In addition, 4 cases were idiopathic (Fig. 2C). The male ratio was 55.4% (n = 650) in the Non-DOC group, while 70.2% (n = 33) in the DOC group. The presence of DOC showed higher incidence in men than in women (70.2% vs. 29.8%, n = 33 vs. n = 14, p = 0.045) (Fig. 3A). The age differed significantly between the groups; in the DOC group, the subjects were older (62.2 ± 18.7 vs. 56.5 ± 17 years, p = 0.025) (Fig. 3C). Supplementary Table 2 shows the data of the 47 cases with DOC. From the nine severe AP, in 3 cases were two episodes seen, from the 13 moderate in 1 case could be two episodes detected, while in the 25 mild cases, no one had two episodes. Regarding the time of onset, an analysis with the Fisher test was performed, which showed no significant difference (p = 0.321) as to whether DOC started on the first day or other days of hospital stay.

Demographic characteristics in ALC DOC vs. Non-ALC DOC groups

From the registered 47 patients with DOC, 23 (48.9%) cases were ALC DOC, whereas 24 (51.1%) cases were Non-ALC DOC (Fig. 2B). In the ALC DOC group, the delirium was present more often than in the Non-ALC DOC group (n = 12 vs. n = 7), while in the Non-ALC
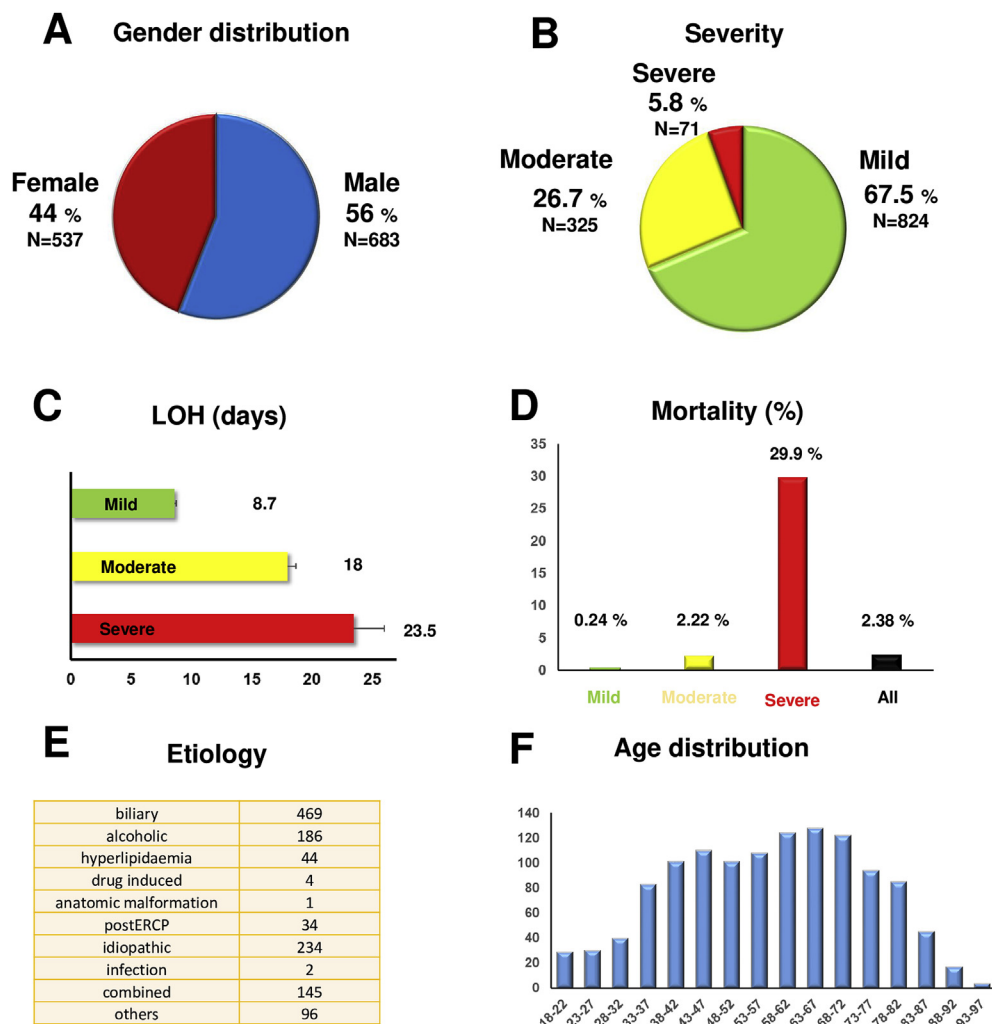

Fig. 1. A. Overall gender distribution. 1.B. Distribution based on severity. 1.C. The average length of hospitalization in days. 1.D. Overall mortality and mortality based on severity classes. 1.E. Distribution based on the etiology of acute pancreatitis. 1.F. Age distribution of the population.
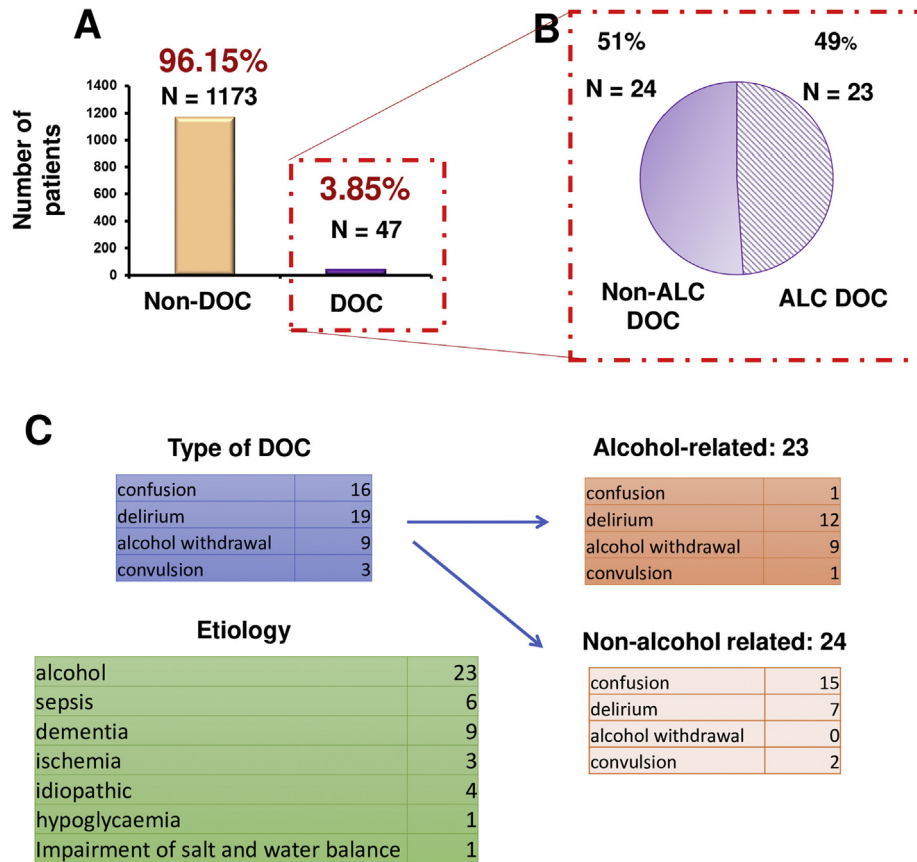
Fig. 2. A Distribution of disturbance of consciousness (DOC) of patients with acute pancreatitis (n). 2.B Distribution of alcohol-related DOC (ALC DOC) and non-alcohol related DOC (Non-ALC DOC) (n). 2.C Distribution of DOC based on type and etiology (n).

group, the confusion with milder clinical features was more often present (n = 15) (Fig. 2C). ALC DOC showed a significant correlation with gender. It developed more frequently in men than women (91.3% vs. 8.7%; n = 21 vs. n = 2; p = 0.002), while in Non-ALC DOC, no difference was seen between the genders (Fig. 3B). Patients with Non-ALC DOC were older than patients with ALC DOC (70.5 ± 18.4 vs. 53.5 ± 15 years, p = 0.002) (Fig. 3D).

Severity and mortality of AP and LOH in DOC vs. Non-DOC groups

Analysis between the DOC and Non-DOC groups showed higher incidence of severe AP (19.2% vs. 5.3%,. n = 9/47 vs. n = 62/1173, p < 0.001) (Fig. 4A), 8.8 times higher mortality (14.9% vs. 1.7%, n = 7/47 vs. n = 20/1173, p < 0.001) (Fig. 4C), and a longer LOH in the DOC group (Me = 11; IQR: 8–17 days vs. Me = 9; IQR: 6–13 days, p = 0.049) (Fig. 4E) respectively.

Severity and mortality of AP and LOH in ALC DOC vs. Non-ALC DOC groups

Moderate AP developed more frequent in patients with ALC DOC vs. Non-ALC DOC group (43.5% vs. 12.5% n = 10 vs. n = 3) while the incidence of severe AP was 7 times higher in Non-ALC vs. ALC DOC group (33.3% vs. 4.4%, n = 8 vs. n = 1), p < 0.001 (Fig. 4B). Mortality showed no difference between the analyzed groups (n = 3 vs. n = 4) (Fig. 4D). Concerning the LOH, patients with Non-ALC DOC showed a tendency for longer hospitalization (Me: 13; IQR: 7–20 days vs. Me: 9.5; IQR: 8–15.5 days, p = 0.119) (Fig. 4F).

Discussion

Nurses and the medical staff have an essential role in recognizing the early signs of changes in mental status and in preventing delirium [14]. However, the hospital-acquired delirium often remains unnoticed, because its symptoms resemble dementia and depression, further complicating the diagnosis [15]. Not surprising that no data is available concerning the relationship of DOC and the outcome of AP.

Here we show for the first time that DOC is associated with more severe and higher mortality rates of AP. The question arises, which factor comes first, the severe AP, or the DOC. It is possible that due to AP released metabolic mediators, hypovolemia and systemic inflammatory response syndrome may lead to different organ failures, such as encephalopathy. On the other hand, in a patient with chronic alcohol consumption during hospitalization with mild AP (based on Atlanta classification), delirium tremens may occur, which is a severe illness in itself, which can lead to multi-organ failure, ICU admission, and mechanical ventilation. It is also important to mention that the development of delirium increases the mortality risk in the intensive care unit (ICU), and it is also associated with longer ICU-stay [16]. A systematic review found that multi-component implementation programs with strategies, targeting ICU delirium assessment, prevention, and adequate treatment including pain, agitation and delirium management, and a strategy of early awakening, breathing, delirium screening, and early exercise have a clinical outcome improving potential [17].

Furthermore, we found that moderate pancreatitis is more common in the ALC DOC group, whereas in the Non-ALC DOC
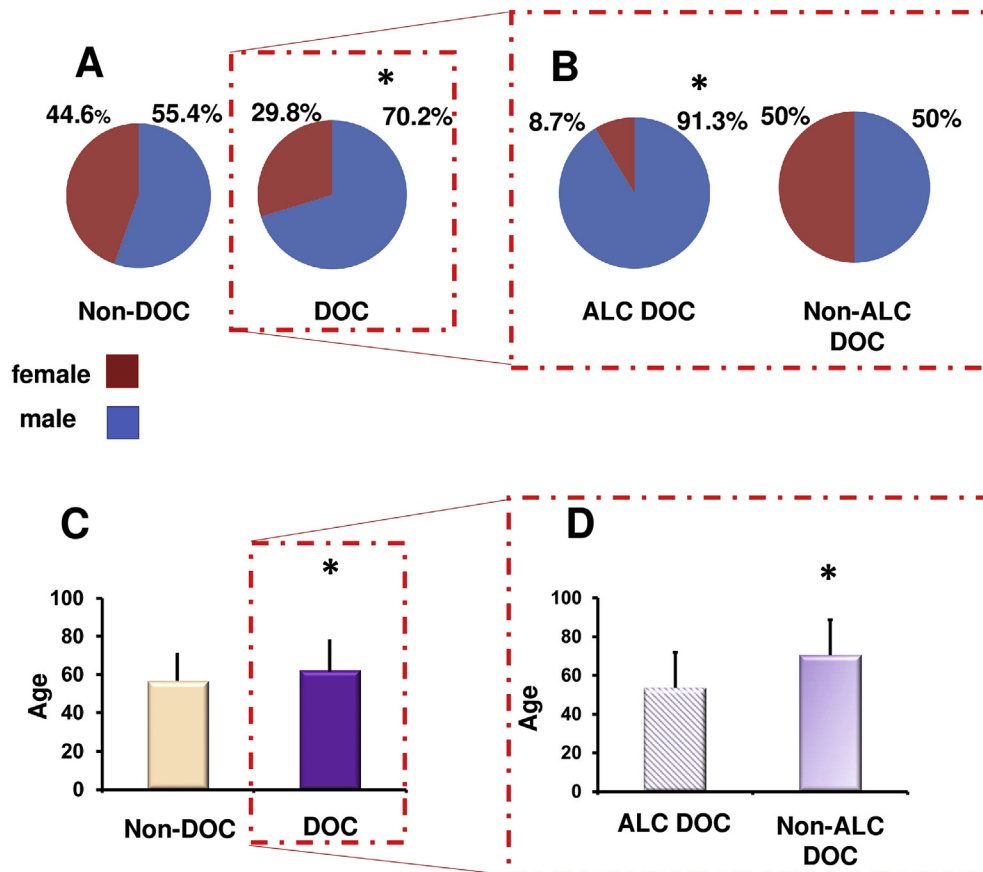
Fig. 3. A Sex distribution of disturbance of consciousness (DOC) and Non-DOC groups (Compared with Chi-squared test). Fig. 3B Sex distribution of alcohol-related DOC (ALC DOC) and non-alcohol related (Non-ALC DOC) groups (Compared with Fisher-test). 3.C Age distribution of DOC and Non-DOC groups (Compared with independent sample *t*-test). 3.D. Age distribution of ALC DOC and Non-ALC DOC groups (Compared with independent sample *t*-test).

group, more severe cases were detected. There was no difference in the mortality rate in the ALC DOC and Non-ALC DOC groups. However, there was a lower rate of severe AP in the ALC group; it had the same mortality rate. This difference may be explained by the fact that, in the ALC DOC group, chronic alcohol consumption is higher. These individuals are of lower social standing, with lower income, often malnourished, have vitamin deficiencies, cachexia/sarcopenia, and are at various stages of liver cirrhosis, all of which can lead to higher mortality in moderate AP. The other suggestion is that DOC influences mortality regardless of etiology.

The findings of this study have some limitations. Based on the cohort analysis, there was a difference in the demographic parameters, which may influence our results. Also, between the DOC and Non-DOC and between the ALC and Non-ALC DOC groups' differences in gender were seen; however, in the ALC DOC group, the gender distribution in alcoholic AP confirms these results. In the DOC and Non-ALC DOC groups, the average age is higher, which may have a causal role in the more severe course of the disease. Besides, based on the analysis method, no conclusion, according to the casualty of DOC and severity could be shown, only associations between the parameters can be provided.

As a clinical implication, according to our data, we can conclude that the onset of DOC is a negative prognostic factor in the outcome of AP. To answer this clinical question, it is necessary to organize an observational clinical trial to monitor all relevant parameters for DOC continuously. This observational clinical study could prove the real causal relationship between DOC and the outcomes of AP. Furthermore, if the observational study confirms our data,

randomized clinical trials aiming to prevent DOC should be organized.

Our data suggest that reducing the development of delirium should be part of the management of AP. A meta-analysis of randomized controlled studies suggests that dexmedetomidine could be a therapeutic option [18]. Benzodiazepines are currently in the first-line treatment for alcohol withdrawal syndrome. They significantly reduce the risk of recurrent seizures related to alcohol withdrawal compared to placebo [19]. In the case of older adults and liver disease, the half-life of diazepam increases with its accumulation and results in a higher rate of side effects. In the elderly and patients with cirrhosis or severe liver dysfunction, lorazepam or oxazepam are preferred [20]. It is pivotal to recognize the symptoms of benzodiazepine toxicity because it leads to respiratory depression, confusion, and delirium through excessive sedation, which may be challenging to differentiate from delirium tremens. In older critically ill patients, polypharmacy may also play an essential role in developing delirium [21]. In the United Kingdom, the Prevention of Delirium system was implemented and delivered in several wards with a staff training program, and they found it feasible [22]. Despite the high prevalence rate of delirium and the marked deteriorating effects on the outcome of the different illnesses, the management of delirium lacks unified professional guidelines.

Conclusions

Disturbance of consciousness is associated with a more severe
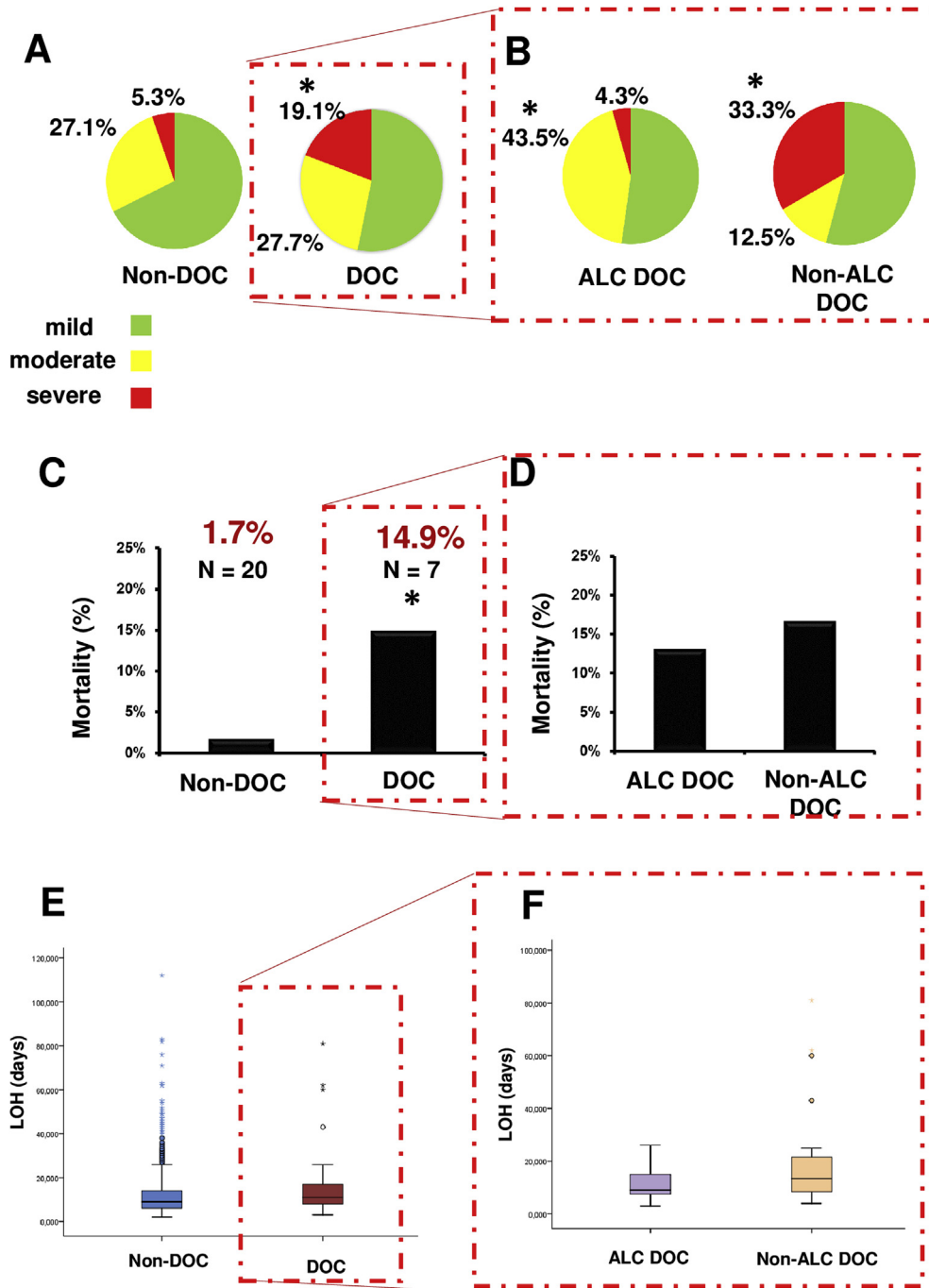
Fig. 4. A Distribution of severity of pancreatitis in disturbance of consciousness (DOC) and Non-DOC groups (Compared with Fisher test). 4.B Distribution of severity of acute pancreatitis of alcohol-related DOC (ALC DOC) and non-alcohol related (Non-ALC DOC) groups (Compared with Fisher test). 4.C Distribution of mortality of DOC and Non-DOC groups (Compared with Fisher test). 4.D Mortality distribution of ALC DOC and Non-ALC DOC groups (Compared with Fisher test). 4.E Distribution of length of hospitalization (LOH) in DOC and Non-DOC groups (Compared with Mann-Whitney test). 4.F Distribution of LOH in ALC DOC and Non-ALC DOC groups (Compared with Mann-Whitney test).

course of AP, longer LOH, and higher mortality rate of the underlying disease. Alcohol consumption in medical history elevates the rate of moderate AP in the DOC group.

Declaration of competing interest

The authors declare that there is no conflict of interest in any consideration.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.05.009.

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