Challenges in gastroenterological emergencies: Outcome prediction in GI bleeding and acute pancreatitis

Ph.D. Thesis

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

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II. Roland Hágendorn, Nelli Farkas, Áron Vincze, Zoltán Gyöngyi, Dezső Csupor, Judit Bajor, Bálint Erőss, Péter Csécsei, Andrea Vasas, Zsolt Szakács, László Szapáry, Péter Hegyi, Alexandra Mikó. Chronic kidney disease severely deteriorates the outcome of gastrointestinal bleeding: A meta-analysis. WORLD JOURNAL OF GASTROENTEROLOGY 23 : 47 pp. 8415-8425. , 11 p. (2017) IF: 3.34

PUBLICATIONS NOT CLOSELY RELATED TO THE SUBJECT OF THE THESIS

1. Dalma Dobszai, Péter Mátrai, Zoltán Gyöngyi, Dezső Csupor, Judit Bajor, Bálint Erőss, Alexandra Mikó, Lajos Szakó, Ágnes Meczker, Roland Hágendorn, Katalin Márta, Andrea Szentesi, Péter Hegyi: Body-mass index correlates with severity and mortality in acute pancreatitis: A meta-analysis. WORLD JOURNAL OF GASTROENTEROLOGY 25 : 6 pp. 729-743. , 15 p. (2019) IF: 3.3

2. Párniczky Andrea, Lantos Tamás, Tóth Eszter Margit, Szakács Zsolt, Gódi Szilárd, Hágendorn Roland, Illés Dóra, Koncz Balázs, Márta Katalin, Mikó Alexandra, Mosztbacher Dóra, Németh Balázs Csaba, Pécsi Dániel, Szabó Anikó, Szücs Ákos, Varjú Péter, Szentesi Andrea, Darvasi Erika, Erőss Bálint, Izbéki Ferenc, Gajdán László, Halász Adrienn, Vincze Áron, Szabó Imre, Pár Gabriella, Bajor Judit, Sarlós Patrícia, Czimmer József, Hamvas József, Takács Tamás, Szepes Zoltán, Czakó László Hegyi Péter. Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations PANCREATOLOGY 19 : 4 pp. 488-499. , 12 p. (2019) IF: 3.629

3. Szakács Zsolt, Gede Noémi, Gyöngyi Zoltán, Solymár Margit, Csupor Dezső, Erőss Bálint, Vincze Áron, Mikó Alexandra, Vasas Andrea, Szapáry László, Dobszai Dalma, Balikó Viktória, Hágendorn Roland, Hegyi Péter, Bajor Judit. Szakács Zsolt, Gede Noémi, Gyöngyi Zoltán, Solymár Margit, Csupor Dezső, Erőss Bálint, Vincze Áron, Mikó Alexandra, Vasas Andrea, Szapáry László, Dobszai Dalma, Balikó Viktória, Hágendorn Roland, Hegyi Péter, Bajor Judit. A call for research on the prognostic role of follow-up histology in celiac disease: a systematic review FRONTIERS IN PHYSIOLOGY 10 Paper: 1408 , 21 p. (2019) IF: 3.16

4. Gódi Szilárd, Erőss Bálint, Gyömbér Zsuzsanna, Szentesi Andrea, Farkas Nelli, Párniczky Andrea, Sarlós Patrícia, Bajor Judit, Czimmer József, Mikó Alexandra, Márta Katalin, Hágendorn Roland, Márton Zsolt, Verzár Zsófia, Czakó László, Szepes Zoltán, Vincze Áron, Hegyi Péter. Centralized Care

For Acute Pancreatitis Significantly Improves Outcomes. JOURNAL OF GASTROINTESTINAL AND LIVER DISEASES 27 : 2 pp. 151-157. , 7 p. (2018) IF: 2.21

5. Szapáry László, Tinusz Benedek, Farkas Nelli, Márta Katalin, Szakó Lajos, Meczker Ágnes, Hágendorn Roland, Bajor Judit, Vincze Áron, Gyöngyi Zoltán, Mikó Alexandra, Csupor Dezső, Hegyi Péter, Erőss Bálint. Intralesional steroid is beneficial in benign refractory esophageal strictures: A meta-analysis
WORLD JOURNAL OF GASTROENTEROLOGY 24 : 21 pp. 2311-2319. , 9 p. (2018) IF: 3.34

6. Gódi Sz, Márta K, Pécsi D, Szabó A, Varjú P, Mikó A, Bajor J, Czimmer J, Hagendorn R, Pakodi F, Pár G, Sarlós P, Szabó I, Vincze Á, Kui B, Illés D, Szentesi A, Pavlovics A, Hegyi P. Acute pancreatitis should be treated in high volume specialist centres. PANCREATOLOGY 17 : 3S p. S108 (2017) IF: 3.629

7. Marta K, Szabo AN, Pecsi D, Varju P, Bajor J, Godi S, Sarlos P, Miko A, Szemes K, Papp M, Tornai T, Vincze A, Marton Z, Vincze PA, Lanko E, Szentesi A, Molnar T, Hagendorn R, Faluhelyi N, Battyani I, Kelemen D, Papp R, Miseta A, Verzar Z, Lerch MM, Neoptolemos JP, Sahin-Toth M, Petersen OH, Hegyi P. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ OPEN 7 : 9 Paper: e015874 , 10 p. (2017) IF: 2.42

8. Kenyeres P, Hagendorn R, Márton Zs, Halmosi R, Gaszner B, Toth K, Habon T. Tachycardia induced heart failure complicated with ventricular thrombus in a young patient with Friedreich's ataxia and cardiomyopathy. EUROPEAN HEART JOURNAL 35 : S1 pp. 1204-1204. , 1 p. (2014) IF: 12.33

9. Tarjányi Zita, Montskó Gergely, Kenyeres Péter, Márton Zsolt, Hágendorn Roland, Gulyás Erna, Nemes Orsolya, Bajnok László, L Kovács Gábor, Mezősi Emese. Tarjányi Zita, Montskó Gergely, Kenyeres Péter, Márton Zsolt, Hágendorn Roland, Gulyás Erna, Nemes Orsolya, Bajnok László, L Kovács Gábor, Mezősi Emese. Free and total cortisol levels are useful prognostic markers in critically ill patients: a prospective observational study. EUROPEAN JOURNAL OF ENDOCRINOLOGY 171 : 6 pp. 751-759. , 9 p. (2014) IF: 5.24

10. Godi Sz, Hágendorn R, Czimmer J, Szabó I, Pakodi F, Vincze A. Godi Sz, Hágendorn R, Czimmer J, Szabó I, Pakodi F, Vincze A. Prospective audit of colonoscopy quality. ZEITSCHRIFT FÜR GASTROENTEROLOGIE 47 : 5 Paper: A27 (2009)

11. Hagendorn R, Dömötör A, Godi Sz, Czimmer J, Hunyady B, Pakodi F, Vincze Á, Szabó I. Retrospective analysis of neddle-knife precut papillotomy in our practice. ZEITSCHRIFT FÜR GASTROENTEROLOGIE 47 : 5 Paper: A30 (2009)

SCIENTIFIC METRICS

Number of publications related to the subject of the thesis:	2 (2 first author)
Cumulative impact factor of publications related to the thesis:	6.969
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Hirsch Index:	6

TABLE OF CONTENTS

List of abbreviations

ABP – acute biliary pancreatitis

ALC-DOC – alcohol-associated disturbance of consciousness

AP – acute pancreatitis

APACHE – Acute Physiology and Chronic Health Evaluation

BISAP – Bedside Index for Severity in Acute Pancreatitis

BMI – body mass index

CI – confidence interval

CKD – chronic kidney disease

CRP – C-reactive Protein

CT – computed tomography

DOC – disturbance of consciousness

eGFR – estimated glomerular filtration rate

ERCP – endoscopic retrograde cholangiopancreatography

ESRD – end-stage renal disease

GAVE – gastric antral vascular ectasia

GFR – glomerular filtration rate

GCS – Glasgow Coma Scale

GI – gastrointestinal

HPSG – Hungarian Pancreatic Study Group

ICU – intensive care unit

LOH – length of hospitalization

MD – mean difference

MOF – multi-organ failure

MRI – magnetic resonance imaging

NOS – Newcastle-Ottawa Scale

OR – odd's ratio

PICO – Patient, Intervention, Comparison, Outcome

PRISMA-P – preferred reporting items for systematic review and meta-analysis protocols

SAP – severe AP

SD – standard deviation

UGIB – Upper GI bleeding

I. General Introduction

In gastrointestinal emergency situations we have to face countless difficulties and challenges. Many of the situation require immediate surgical interventions or intensive care unit (ICU) admission, and for most of them, special scoring systems were defined, to detect the severity of the disease or the worsening condition of the patient.

Acute, severe gastrointestinal (GI) bleeding has previously required predominantly surgical care. Following the introduction and expansion of gastrointestinal endoscopy, the number of cases requiring surgery has dropped significantly. The incidence of upper non-variceal bleeding and the need for operative intervention has been steadily declining since 1993. Although endoscopic modalities have undergone significant development, it can be said that we have not been able to achieve a significant improvement in the mortality of gastrointestinal bleeding in the last decades [1]. Possible reasons are the significant increase in the average age of the population and fatal outcomes due to the many comorbidities associated mostly with old age. It is often seen that GI bleeding can be stopped in a patient, yet the outcome is fatal. Accordingly, a reduction in mortality rates in the future will be possible if patient management, independent of endoscopic techniques can be improved. The key is to have a proper risk assessment and to pay more attention to the treatment of vulnerable patients (early, accurate risk assessment, closer observation, multi-parameter monitoring). There are several risk assessment and outcome predictor scoring systems, most of which rely on clinical parameters typical of the acute phase of bleeding. The Rockall scoring system calculates outcome based on comorbidities, however, e.g. in terms of renal failure, the stages are not properly defined [2].

Acute pancreatitis (AP) is a leading cause of hospital admissions worldwide [3,4]. The disease can be traced back to various causes, which can vary in severity [5,6]. According to the severity of the disease, we distinguish between mild, moderate and severe cases. Mortality in severe cases is much higher, approximately 30% [7]. As the mortality of severe cases is high, the disease has been in the focus of research in recent decades [8]. As a result, there is a significant improvement in mortality, but it is still high. Different scoring systems try to predict the outcome of cases with more or less success. Subsequent complications are not taken into account by these scoring systems. Accordingly, they do not clarify the effect of the case on the outcome. The modified Marshall scoring system takes multiple organ system dysfunctions into account, which are strongly correlated with mortality and ICU admission [9]. Three major organ systems are highlighted i.e., renal, cardiovascular, and respiratory

failure formation are the most frequently researched and articles on topics, while neurological complications and regular use of the Glasgow Coma Scale (GCS) have been pushed into the background. In clinical practice, patients hospitalized for acute pancreatitis may have or may be formed neurological symptoms such as alcohol withdrawal syndrome, confusion and delirium. Disorder of consciousness means the development of spatial and temporal disorientation, it often occurs in hospitalized patients, especially the elderly. The currently used prognostic score systems do not take into account the disturbances of consciousness developed during hospital admission, so they cannot estimate their effect on the course of the disease. Treatment of AP is predominantly supportive, accordingly, if complications can be reduced with adequate patient care, it can also improve the outcome.

II. Pre-existing chronic kidney disease and GI bleeding

II.1 Introduction GI Bleeding

Acute GI bleeding is an abdominal emergency that remains a common cause of hospitalization [10]. An accurate diagnosis of GI bleeding relies on prompt resuscitation, initial risk evaluation, and provisional clinical diagnosis followed by an appropriate definitive investigation that enables specific therapeutic interventions. GI bleeding involves any bleeding in the GI tract from the esophagus, stomach, small intestines or large intestines to the anus.

II.1.1. Clinical features and diagnosis of GI bleeding

Upper GI bleeding (UGIB) has an annual incidence that ranges from 40 to 150 episodes per 100000 persons and a mortality rate of 6%-10% [11]. The main symptoms are haematemesis, melena and hematochezia. The most common causes of upper GI bleeding remains gastroduodenal ulcer disease, erosive esophagitis, gastritis/duodenitis, and esophagogastric varices. In addition to these, some other abnormalities can cause bleeding such as portal hypertensive gastropathy, angiodysplasia (vascular ectasia), Mallory-Weiss syndrome, Dieulafoy's lesion, gastric antral vascular ectasia (GAVE), hemobilia, haemosuccus pancreaticus, aortoenteric fistula, Cameron lesions, ectopic varices, iatrogenic bleeding after endoscopic interventions, gastrointestinal tumors. Endoscopy is highly useful for diagnosing

the cause of UGIB, with 92%–98% sensitivity and 3%–100% specificity, and enables effective treatment of bleeding in the majority of cases [12]. Radiologic methods (computed tomography [CT] angiography) have a role in assessing UGIB only when upper endoscopy is not feasible or yields inconclusive results. Upper GI endoscopy may be contraindicated in the setting of shock, substantial comorbidity, or massive hemorrhage. Adequate endoscopic evaluation of the bleeding source may not be possible when extensive luminal blood obscures visualization or the bleeding originates from a difficult anatomic location such as the distal duodenum. Lower GI bleeding has an annual incidence ranging from 20 to 27 episodes per 100000 persons and a mortality rate of 4%-10% [13, 14]. The most frequent causes of lower GI bleeding in this population have been described; diverticulosis, hemorrhoids, ischaemic colitis, inflammatory bowel disease-associated bleeding, post polypectomy, colon cancer/polyps, rectal ulcer, vascular ectasia, radiation colitis/proctitis.

II.1.2 Therapy

The approach to medications and endoscopy are similar for patients with upper GI bleeding. It is particularly important to ensure that these patients are adequately resuscitated before undergoing upper endoscopy. Traditionally, three endoscopic treatment methods of upper GI bleeding have been used: injection therapy, thermal therapy, and mechanical therapy. If endoscopy fails surgery or interventional radiology are indicated. The accepted medications are acid suppression with proton pump inhibitors, prokinetics, vasoactive medications and antibiotics for patients with liver cirrhosis.

II.1.3 Prediction

Since GI bleeding is a potentially life-threatening acute disorder, understanding the risk factors that worsen the disease is of great importance. Scoring systems have therefore been developed to predict the outcome of therapy. The Rockall score is one of these scoring systems. It includes pre-endoscopic (age, shock and comorbidity) and post-endoscopic (diagnosis and presence or absence of endoscopic stigmata of recent hemorrhage) factors [2]. Several studies have demonstrated high mortality with higher Rockall scores [15]. However, Laeeq et al. [16] have not found significantly higher mortality in patients with high pre-endoscopic Rockall score (> 5). The Rockall score only assesses the risk of mortality in patients with upper GI bleeding. The Glasgow Blatchford score is another scoring system that uses clinical and laboratory parameters [17]. Neither scoring system makes a distinction between pre-existing renal failure and acute renal failure due to haemorrhage. The Rockall

score takes into account renal failure for comorbidities but does not differentiate the degree of renal failure. The Glasgow Blatchford score system evaluates the incoming renal function value but does not differentiate between acute and chronic renal failure. Both of these scoring systems have been designed for the risk assessment of upper GI bleeding. The newer AIMS65 Score was designed to predict mortality in adults presenting with acute upper GI bleeding. It does not use renal function abnormalities in risk assessment [18].

Glasgow-Blatchford Scoring System			
BUN (mg/dL)	<18	0	**BUN (mmol/L)**
	18-22	2	6.5-<8
	23-27	3	8-<10
	28-70	4	10-<25
	>70	6	>25
Hemoglobin (men, g/dL)	>13	0	
	12-12.9	1	
	10-11.9	3	
	<10	6	
Hemoglobin (women, g/dL)	>12	0	
	10-11.9	1	
	< 10	6	
Systolic blood pressure (mmHg)	> 110	0	
	100-110	1	
	90-99	2	
	< 90	3	
Other markers	Pulse > 100 bpm	1	
	Presentation of melena	1	
	Presentation of syncope	2	
	Hepatic disease	2	
	Cardiac failure	2	

Rockall Scoring System				
Variable	**Score=0**	**Score =1**	**Score =2**	**Score =3**
Age (years)	<60	60-79	>80	
Comorbidity			Congestive heart failure, ischemic heart disease	Renal failure, liver disease, metastatic disease
Shock	No shock	Pulse > 100 bpm	Systolic BP <100 mmHg	
Source of bleeding	Mallory-Weiss Tear	All other diagnoses: e.g., esophagitis, gastritis, peptic ulcer disease, varices	Malignancy	
Stigmata of recent bleeding	None		Adherent clot or spurting vessel	

AIMS65 Score	
Variable	Score
Albumin <3 g/dL	1
INR >1.5	1
Systolic BP <90 mmHg	1
Altered Mental Status	1
Age >65 yr	1

Table 1. The Glasgow-Blatchford, Rockall and AIMS65 scoring system. [19]

II.1.4 CKD/ESRD

CKD is defined by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause. The persistence of the damage or decreased function for at least three months is necessary to distinguish CKD from acute kidney disease. Decreased kidney function refers to a decreased glomerular filtration rate (GFR), which is usually estimated (eGFR) using serum creatinine. [20] The most common causes of CKD are diabetes mellitus, drug toxicity, auto-immune diseases, urinary tract obstruction, kidney transplantation etc. CKD is classified based on the eGFR and the level of proteinuria. Patients are classified as G1-G5, based on the eGFR. Previous studies have shown evidence of increased risk of GI bleeding in CKD patients and with end-stage renal disease (ESRD) requiring renal replacement therapy in comparison with the general population, but also an association with higher mortality [21-23]. Further studies have demonstrated that bleeding in CKD patients from the upper GI tract is more common than from the lower GI tract [24]. The increased prevalence of small bowel erosions, ulcers and angioectasias is also well known in CKD patients and it may be as high as 33% and it often causes obscure gastrointestinal bleeding [25-27]. However, no meta-analyses or systematic reviews have been conducted to assess the difference between CKD/ESRD patients and the normal renal function population concerning GI bleeding.

CKD Stages and Associated Estimated Glomerular Filtration Rate (eGFR)	
CKD Stage	***eGFR Level***
Stage 1 (normal)	Above 90 ml/min
Stage 2 (mild)	60-89 ml/min
Stage 3 (moderate)	30-59 ml/min • Stage 3A 45-59 ml/min • Stage 3B 30-44 ml/min
Stage 4 (severe)	15-29 ml/min
Stage 5 (failure, ESRD)	Below 15 ml/min

Table 2. CKD stages [28].

II.2 Hypotheses

Pre-existing CKD may worsen the prognosis in GI bleeding. We performed this meta-analysis to compare CKD patients and normal renal function patients based on GI bleeding. We investigated these two groups in terms of mortality, transfusion amount, rebleeding rate and length of hospitalization.

II.3 Materials and methods

II.3.1 Search strategy

This study was conducted using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) [29]. It was registered in the international prospective register of systematic reviews, PROSPERO (under registration number CRD42017077987). The meta-analysis was based on the PICO (Patient, Intervention, Comparison, Outcome) format (P: patients with GI bleeding; I: chronic renal failure; C: normal renal function; O: mortality, blood transfusion, rebleeding). A systematic search was performed in 3 databases, Pubmed, EMBASE and the Cochrane Library, with the following terms: (“GI bleeding” OR “gastrointestinal bleeding” OR “gastrointestinal hemorrhage”) AND (“chronic renal failure” OR “uremia” OR “chronic kidney failure”). The search was limited to human data and to full-text English-language articles if appropriate. The exact search term in Pubmed was: [“GI bleeding”(All Fields) OR “gastrointestinal bleeding”(All Fields) OR “gastrointestinal

hemorrhage"(All Fields)] AND ["chronic renal failure"(All Fields) OR "uraemia"(All Fields) OR "uremia"(MeSH Terms) OR "uremia"(All Fields) OR "chronic kidney failure"(All Fields)] AND ["humans"(MeSH Terms) AND English(lang)]. The database search was conducted up to 10 March 2017. Reference management software (EndNote X7) was used to remove duplicates by searching overlaps between titles, authors and publication years. The reference lists in the articles obtained were also checked, and one more eligible publication was found.

II.3.2 Study selection

The studies were selected separately by two investigators (RH and AM). Disagreements were resolved by consulting a third reviewer (PH). Clinical studies were eligible provided they reported data on adult patients hospitalized with upper or lower GI bleeding grouped into normal renal function and CKD or ESRD groups. Articles were eligible containing data of CKD/ESRD patients and a control group in the same study. Information on mortality, transfusion, rebleeding and length of hospitalization (LOH) was manually searched. Case reports, conference abstracts, reviews and studies on pediatric patients up to age 18 alone were excluded. We found a high number of articles in which the risk of GI bleeding in CKD patients was studied, but they were not eligible for our meta-analysis, as there were no data available on outcomes of the GI bleeding in a control population without CKD/ESRD.

II.3.3 Data extraction, synthesis and analysis

Mortality data, number of transfused blood units, rebleeding and length of hospitalization data were extracted to analyse the influence of CKD and/or ESRD on the outcome of GI bleeding. In Sood et al [23], Tsai et al [30] and Boyle et al [31], the number of patients was calculated from percentages of mortality. Boyle et al[31] supplied information on transfusion in mean and standard error of mean, for which statistical calculation standard deviation (SD) was computed. Tsai et al [30] reported data from transfusions in the median and interquartile range, from which mean and SD were calculated with Hozo's method[32]. All meta-analytic calculations were performed with Comprehensive Meta-Analysis software (Version 3.0, Biostat Inc.) using the random-effects model (DerSimonian-Laird method[19]). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for binary outcomes. In the case of LOH and transfusion for comparing mean data, a mean difference (MD) with 95%CI was calculated. All analyses were two-tailed, with an α of 0.05.

Heterogeneity was tested using Cochrane's *Q* and the *I*2 statistics. Based on the Cochrane Handbook, $I2 = 100\% \times (Q - df)/Q$, with *I*2 representing the magnitude of the heterogeneity (moderate: 30%-60%; substantial: 50%-90%; considerable: 75%-100%) [33]. Only results that were available from at least 3 studies were displayed graphically with forest plots. We performed a sensitivity analysis to assess whether removing any study results in different interpretations and final conclusions [21]. To assess the effect of the year of publication on the outcome data we performed meta-regression analysis. We calculated the regression coefficient and interpreted the data with their 95%CI and r-analog.

II.3.4 Quality of studies and risk of bias

Because of the low number of eligible articles, publication bias was obtained with a visual inspection of the funnel plots alone according to the Cochrane Handbook [33]. The Newcastle-Ottawa Scale (NOS) adjusted to our study design was used [34] to assess the quality of nonrandomized cohort studies. The selection, comparability and outcome data were assessed based on 6 items (Table 3) with the "star system": high-quality items with a low risk of bias received one star, while low-quality items with a high or unknown risk of bias were assigned no stars.

Adapted Newcastle-Ottawa Scale Items	High-quality items carrying a low risk of bias (green)	Low-quality items carrying a high (red) or an unknown (yellow) risk of bias
Item 1: Representativeness of the initial study population - patients with GI bleeding and CKD/ESRD	All patients with upper or lower GI bleeding and CKD/ESRD were included.	Low: any selection criteria were applied to the study population (*e.g.*, only transplanted patients). Unknown: no data on selection process.
Item 2: Representativeness of the initial study population - patients with GI bleeding without CKD/ESRD	All patients with upper or lower GI bleeding without CKD/ESRD included.	Low: any selection criteria were applied to the study population. Unknown: no data on selection process.
Item 3: Ascertainment of exposure	We defined chronic renal failure as present when eGFR was < 60 mL/min at least 3 mo. We defined end-stage renal disease as a condition where hemodialysis or chronic peritoneal dialysis is performed at least for 3 mo.	Low: CKD or ESRD is not present in all of the patients. Unknown: no definitions of the conditions mentioned are provided.
Item 4: Comparability of cohorts A	Study controls for age: no significant difference was detected.	Low: significant difference was detected. Unknown: no statement.
Item 5: Comparability of cohorts B	Study controls for taking ulcerogenic drugs: no significant difference was detected	Low: significant difference was detected between taking ulcerogenic drugs. Unknown: no comparison made by taking ulcerogenic drugs.
Item 6: Follow-up time for rebleeding	The follow-up time is clearly defined.	Low: incomplete follow-up Unknown: no follow-up time is mentioned.

Table 3. Modified Newcastle-Ottawa Scale criteria.

3 items were included during the selection process. In the case of representativeness in the study population, we assigned a star if all of the GI bleeding patients with normal or impaired renal function were included. If any selection criteria were applied, we assigned no points. We used the classical definition of CKD [35], which characterizes the disease with a glomerular filtration rate (GFR) < 60 ml/min lasting longer than 3 mo. ESRD was defined as a condition where hemodialysis or chronic peritoneal dialysis is performed for at least 3 mo. Concerning outcome, only the follow-up time for rebleeding was rated in articles that provided this information. Assessment of outcome and length of follow-up were not rated because most of the articles were retrospective.

II.4 Results

II.4.1 Study selection

1063 articles (EMBASE: 589; PubMed: 459; Cochrane: 15) were found altogether through database searches. The flowchart (Figure 2) shows the study selection strategy.

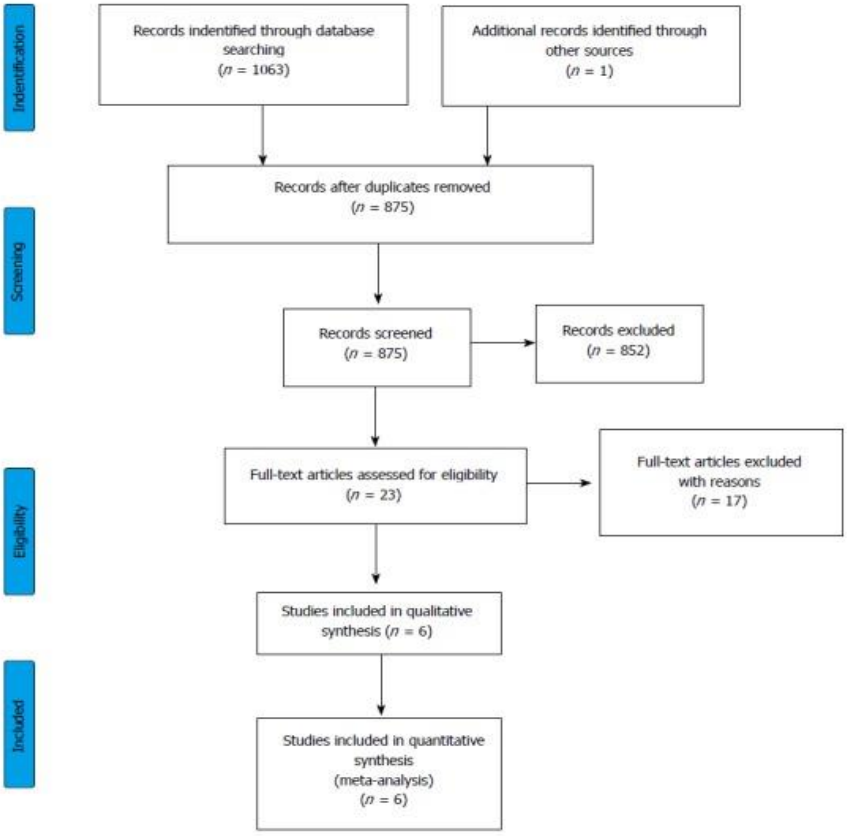


Figure 2. The flowchart of the study selection procedure.

Studies in our meta-analysis were dated from 1946 to 2017. After removing duplicates, 875 publications remained. Following initial screening based on titles and abstracts, 23 articles were retrieved and screened. A further 18 were excluded because of missing outcome data or a missing control group. Patients with acute renal failure were also included in the analysis reported in Alvarez et al [36], so we did not use the data in that publication. The remaining 5 [23, 30, 31, 37, 38] and one other [21] eligible record which was found in reference lists were included in the meta-analysis. The basic characteristics of the 6 eligible articles in the meta-analysis are shown in Table 4.

Ref.	Country	Study type	Years of study	Group	Sample size	Age	Mortality	Transfusion	Rebleeding	Length of hospitalization
Boyle *et al*[17], 1983	United States	Retrospective	1977-1981	Control	40	54 ± 2[1]	√	√	-	√
				CKD (mix)	20	59 ± 4[1]				
Cheung *et al*[20], 2010	Canada	Retrospective	2000-2006	Control	50	67 ± 13	√	√	√	√
				CKD	50	71 ± 13				
				ESRD	50	68 ± 12				
Hung *et al*[23], 2014	Taiwan	Retrospective	2007	Control	6322	54.6 ± 13.3	√	-	-	-
				ESRD	110	NR				
Sood *et al*[9], 2012	United States	Retrospective	2007	Control	347245	NR	√	-	-	-
				CKD	35985	NR				
				ESRD	14983	NR				
Tsai *et al*[16], 1996	Taiwan	Prospective	1991-1994	Control	640	55.7 ± 16.2[2]	√	√	√	-
				ESRD	58	64.1 ± 11.4[2]				
Zuckerman *et al*[26], 1985	United States	Retrospective	1980-1983	Control	423	63 (16-96)[3]	-	-	√	-
				CKD (mix)	59	57 (24-84)[3]				

Table 4. Basic characteristics of the studies included in the meta-analysis.

These 6 publications contained data on 406,035 patients, of whom 51315 had impaired renal function parameters and 354720 had normal renal functions. 2 articles contained data on patients with CKD and 4 on ESRD patients. There were 2 studies involving CKD and ESRD patients, with their group identified as the CKD mixed group. The number of ESRD patients analysed was 15201, the CKD group had 36035 members, and 79 patients could be classified in the CKD mixed group.

II.4.2 Mortality

Data on mortality was available in all of the articles included, but Zuckerman et al [38] reported no mortality data for the control group; we, therefore, removed it from the statistical analysis. Hung et al [37] reported mortality data from a 6-wk follow-up period, while the other articles contained data on an unknown follow-up period. In the subgroup analysis for CKD and ESRD, a higher mortality rate was detected compared to the control population (CKD: OR = 1.786, 95%CI: 1.689-1.888, $P < 0.001$; ESRD: OR = 2.530, 95%CI: 1.386-4.616, $P = 0.002$, Figure 3).

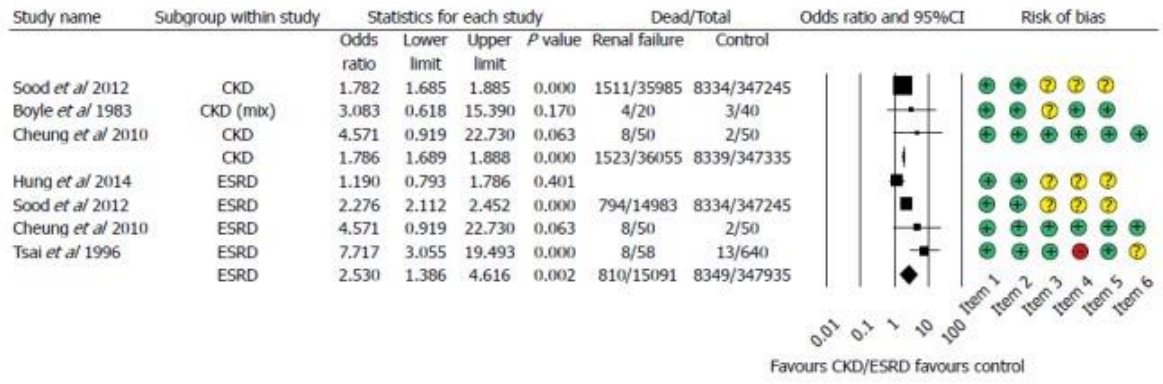


Figure 3. Forest plot representing the differences in mortality in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

II.4.3 Required units for transfusion

4 studies reported data on the transfused units of red blood cells. The required transfusion was 1.8 times higher in the patients with abnormal renal function (MD = 1.863, 95%CI: 0.812-2.915, $P < 0.001$, Figure4).

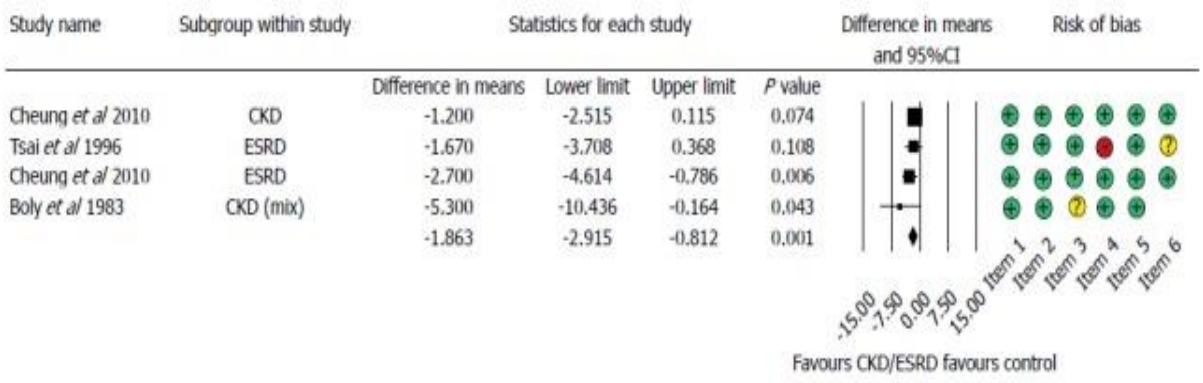


Figure 4. Forest plot representing the required units of transfusion in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for the difference in standardized mean values reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

II.4.4 Rebleeding rate

It was possible to retrieve data on the rebleeding rate from 3 articles, but Cheung et al [21] contained simultaneous data from the CKD and ESDR groups, which could be analysed. Boyle et al [31]. also presented data on rebleeding. However, this included cases of uncontrolled bleeding, so we excluded these data from our analysis. We found that patients with impaired renal function tend to bleed again 2.5 more times than patients with normal renal function (OR = 2.510, 95%CI: 1.521-4.144, $P < 0.001$, Figure5).

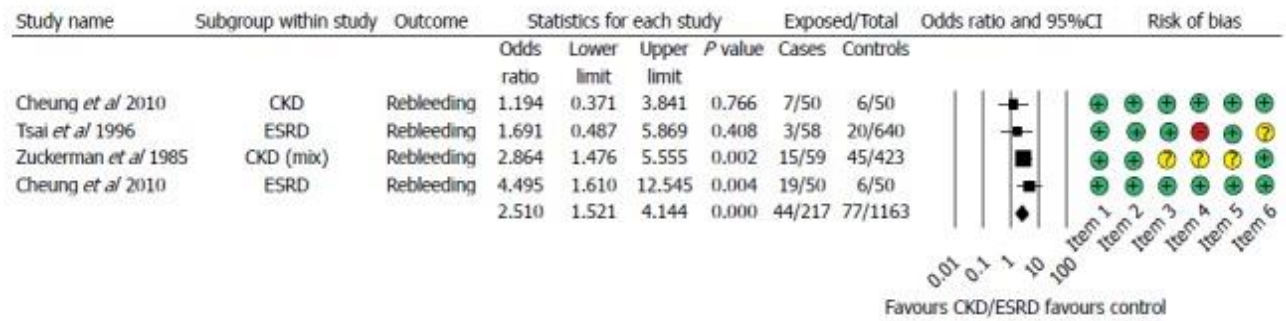


Figure 5. Forest plot representing the rebleeding rate in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

II.4.5 Length of hospitalization

Two of the six articles included reported hospital stay outcomes. Patients with impaired renal function spent significantly more time in hospital after GI bleeding (MD = 13.245, 95%CI: 6.886-19.623, $P < 0.001$, Figure 6).

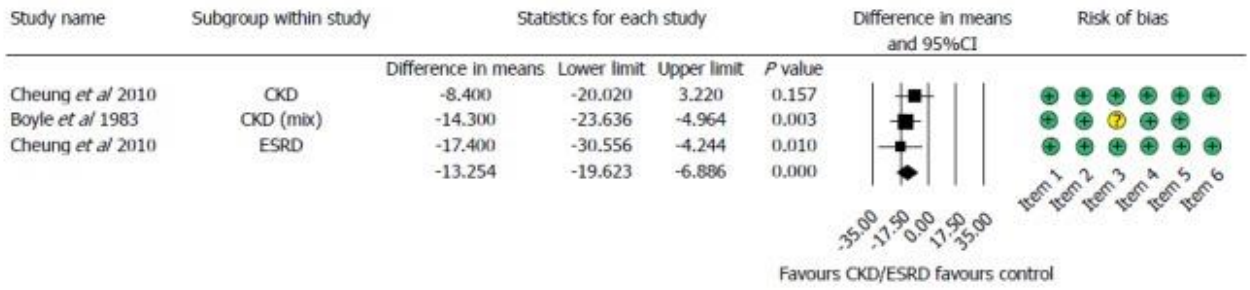


Figure 6. Forest plot representing the differences in length of hospitalization in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for the difference in standardized mean values reflects weight of trial in pooled analysis. Horizontal bars represent 95% CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease

II.4.6 Heterogeneity and quality assessment of data

High heterogeneity was detected for mortality in the ESRD group (Q = 17.082; DF = 3; $I2$ = 82.438%; $P < 0.001$), while the heterogeneity for CKD was low (Q = 1.767; DF = 2; $I2$ = 0%; $P = 0.413$). However, a low heterogeneity was detected for the transfusion requirements (Q = 3.448; DF = 3; $I2$ = 13.003%; $P = 0.328$), the rebleeding rate (Q = 3.328; DF = 3; $I2$ = 9.845%; $P = 0.344$) and LOH (Q = 1.100; DF = 2; $I2$ = 0%; $P = 0.577$). To ascertain publication bias, we only made a visual assessment of the funnel plot (Figure 7) because we were only able to include 6 studies in our meta-analysis.

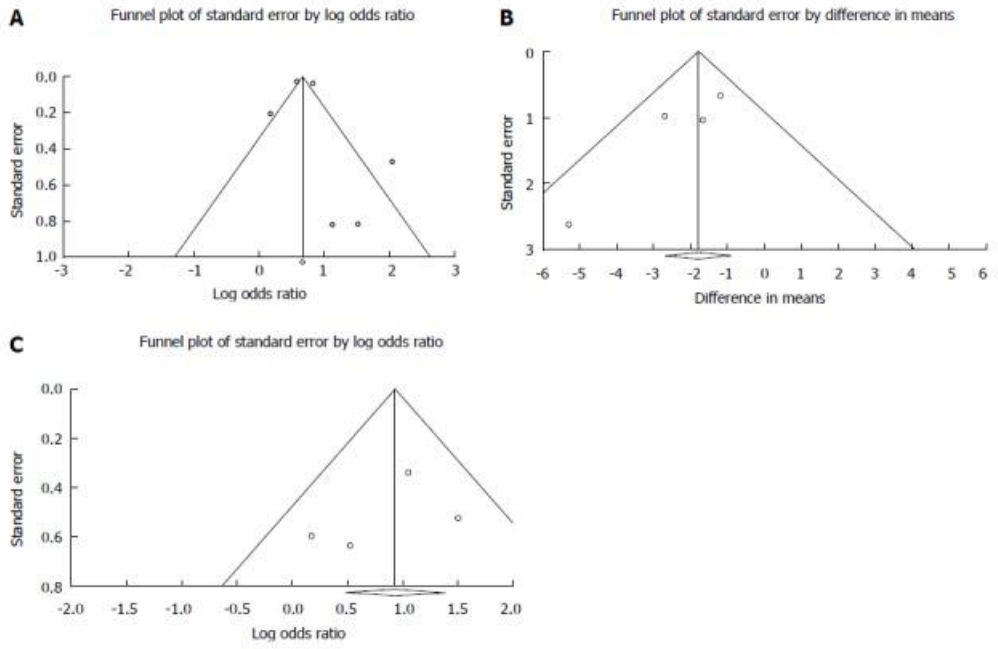


Figure 7*. Funnel plot. A: Funnel plot of mortality; B: Funnel plot of required transfusion; and C: Funnel plot of rebleeding*

Sensitivity analysis showed no significant difference in the OR of mortality, by removing any of the articles (Figure 8).

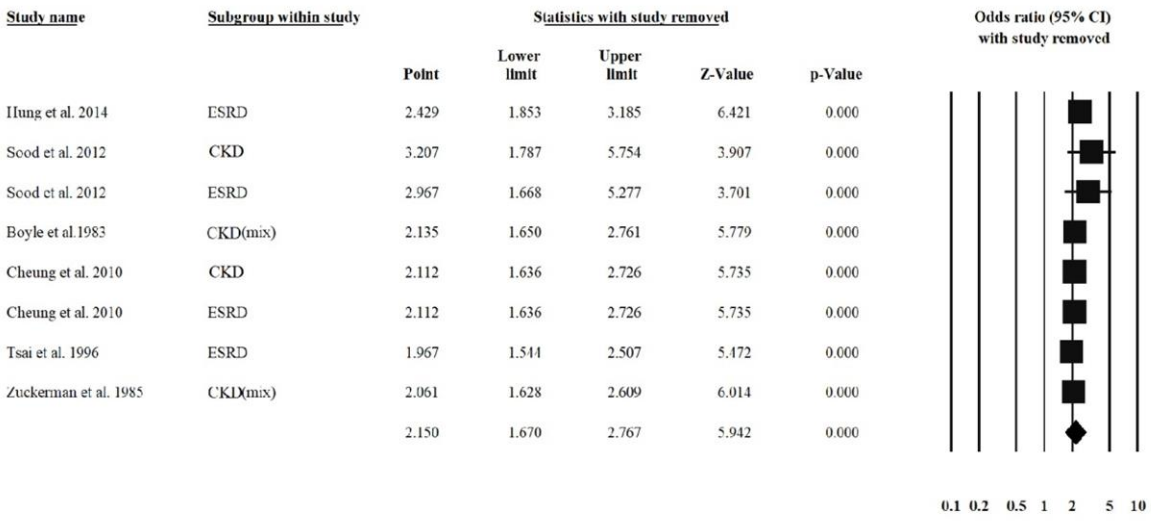
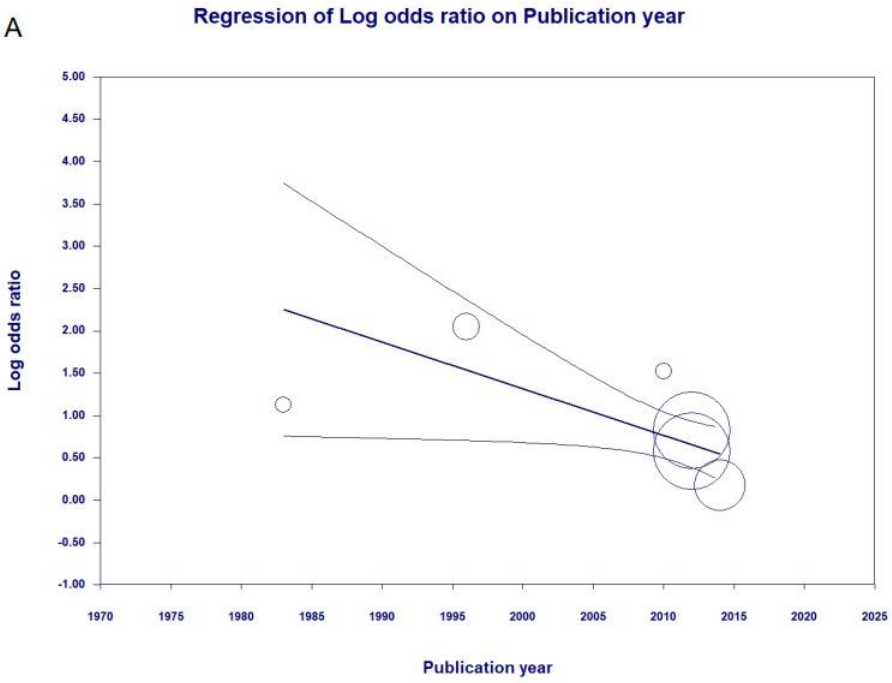


Figure 8: Sensitivity analysis of mortality data

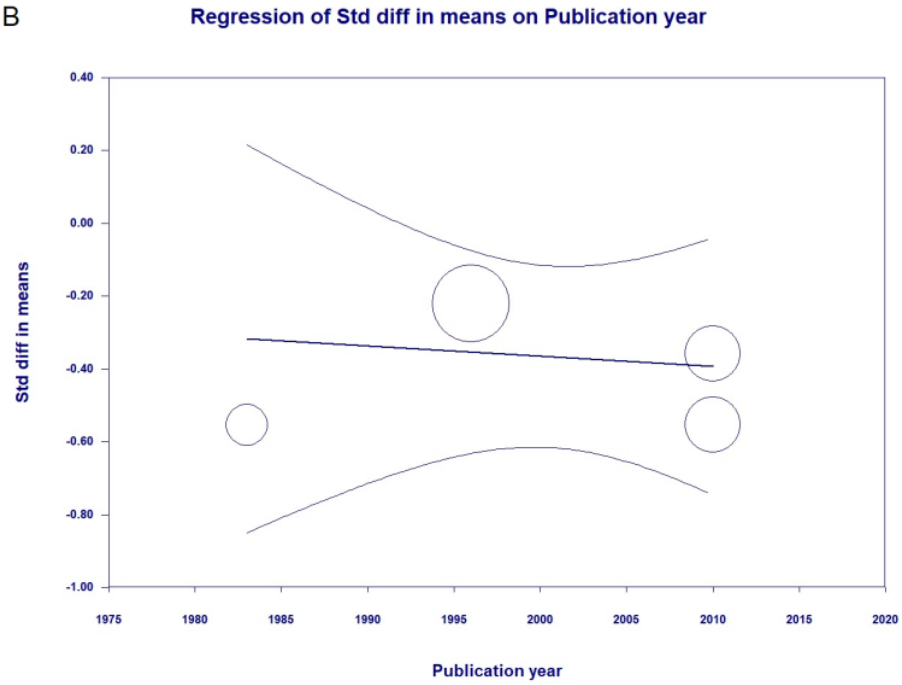
Meta-regression showed slight significance, in the most recent articles the OR is decreasing with the time (regression coefficient: b = -0.0548; 95%CI: -0.0968 to -0.0128; P = 0.0105; r-

analog: 0.2, Figure 9/A. The number of required units for transfusion has not changed since the 1980s (b = -0.0028; 95%CI: -0.0242 to -0.0186; P = 0.7972; r-analog: 0.00, Figure 9/B). Based on data from 4 articles, no difference in rebleeding rate could be observed in the last 30 years (b = 0.0027; 95%CI: -0.0353 to 0.03; P = 0.8726; r-analog: 0.00, Figure 9/C).

A



B



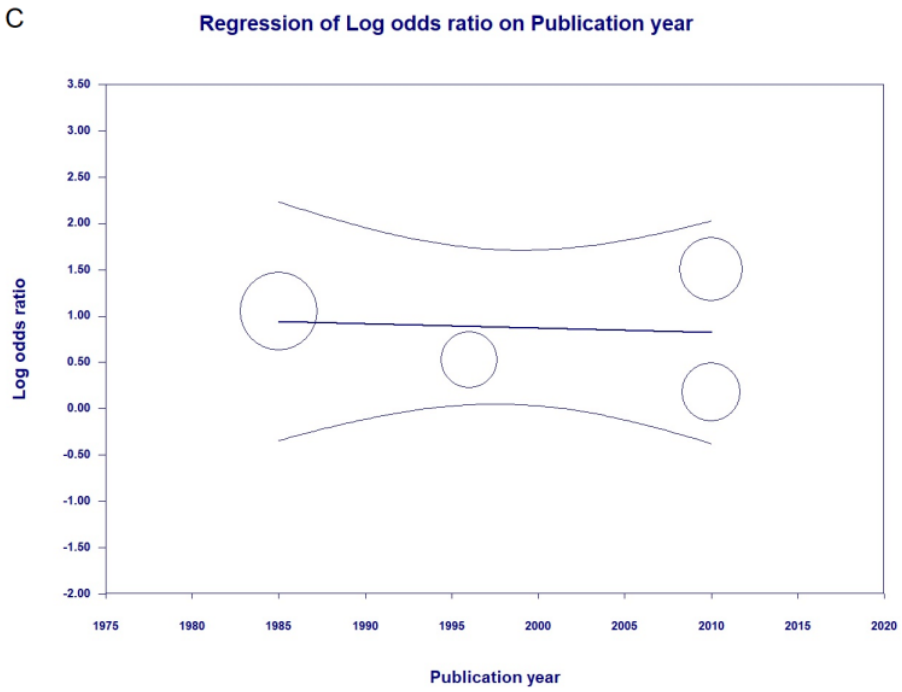


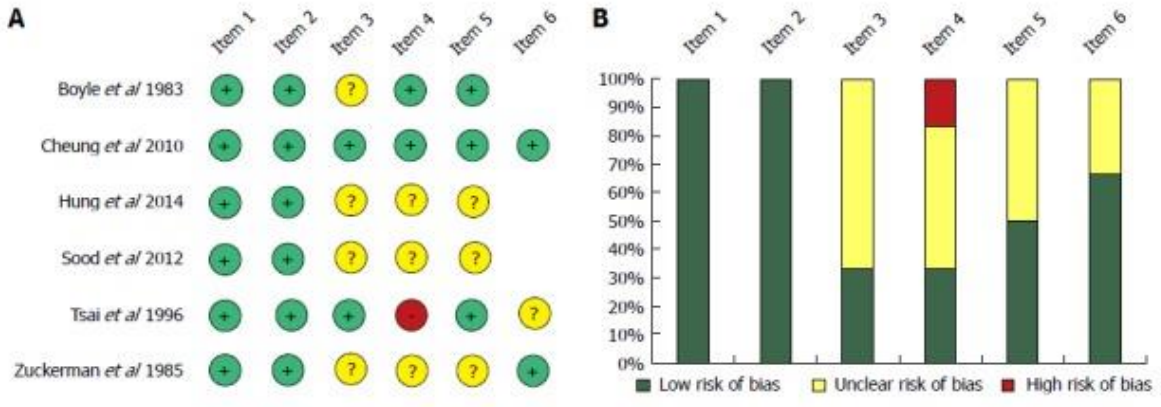
Figure 9. A: Meta-regression of mortality data. B: Meta-regression for rebleeding data. C: Meta-regression for number of required units for transfusion

On the score based on the Newcastle-Ottawa Scale, articles were assigned between 2 and 6 stars out of a maximum of 6 stars (Table 5).

ARTICLE	Item 1.	Item 2.	Item 3.	Item 4.	Item 5.	Item 6.	Total
Boyle et al. 1983	*	*	-	*	*		**4***
Cheung et al. 2010	*	*	*	*	*	*	**6***
Hung et al. 2014	*	*	-	-	-		**2***
Sood et al. 2012	*	*	-	-	-		**2***
Tsai et al. 1996	*	*	*	-	*	-	**4***
Zuckerman et al. 1985	*	*	-	-	-	*	**3***

Table 5. Stars based on the Modified Newcastle–Ottawa Scale

There was a low risk of bias in representativeness in the study and the control population; it received 100% (Figure 10).



(Figure 10). Risk assessment of articles included in the meta-analysis based on the modified Newcastle-Ottawa Scale (A); Risk of bias assessment graph (B).

With regard to ascertaining exposure, 33% of the articles represented a low risk of bias, while 66% had an unclear risk of bias. In these articles CKD and ESRD were not clearly defined, or patients were sorted based on a code system. With regard to a comparison of age, half of the articles contained no clear data on the groups and there was a significant difference in the ages of the ESRD and control groups in Tsai et al [30]. 50% of the articles reported data on taking ulcerogenic drugs; the other half represented an unclear risk of bias. The follow-up time for rebleeding was analysed in 3 articles; only one did not report this clearly.

II.5 Discussion

CKD is a term that covers all degrees of decreased renal function (mild, moderate, and severe chronic kidney disease), where the GFR is lower than 60 mL/min for longer than 3 mo[[35]]. CKD is a worldwide public health problem, with both incidence and prevalence rising and the main causes being diabetes mellitus and high blood pressure. ESRD patients requiring hemodialysis or peritoneal dialysis 3 times a week represent a high burden and cost for the health care system. As the prevalence of hypertension and diabetes mellitus, the most important etiological factors for CKD and ESRD is increasing worldwide, we predict that GI

bleeding with CKD will be a growing problem. According to Ohmori et al [27] the number of patients on hemodialysis has tripled between 1990 and 2010. This is the first meta-analysis to report on the severity of complications after GI bleeding in patients with CKD or ESRD and normal renal function groups. Based on a systematic search in 3 databases, we were able to include 6 articles, which contained data on 406035 patients, of whom 51315 had impaired renal function. A higher prevalence of peptic ulcers was reported among ESRD patients undergoing long-term dialysis[39, 40]. The elevated risk for GI bleeding in CKD and ESRD patients is also well known [41]. The most frequent causes of lower GI bleeding in this population have been described; diverticulosis, hemorrhoids, and ischaemic colitis have been identified in addition to angioectasias [42], but no cohort study has been conducted on this topic yet. Although we did not intend to narrow our search to upper GI bleeding, the articles eligible for our inclusion criteria contained data only on patients with upper GI bleeding, and no studies with lower GI bleeding met our inclusion criteria. Only a few of the studies detailed the endoscopic findings and cause of bleeding. Cheung et al [21] included only peptic ulcer bleeding patients, while the study of Hung et al [37] examined only esophageal variceal bleeding. Tsai et al [30] found that erosive gastritis was significantly higher in ESRD group, while Boyle et al [31] saw gastric ulcer as the most common cause of bleeding in the impaired renal function group, but it was not significant compared to controls. Zuckerman et al [38] found significantly more angiodysplasia and erosive esophagitis in the impaired renal function group.

Based on the pooled data, we found that ESRD increases mortality 2.5 times while CKD increases it 1.8 times in GI bleeding compared to the controls with normal renal function, but these ORs are not significantly different. Weng et al [43] reported that ESRD patients admitted with primary upper GI bleeding have a profoundly increased risk of in-hospital mortality. Using a large multi-center database, Sood et al [23] reported that the in-hospital mortality risk is 50% higher in CKD patients and 3 times greater in ESRD patients. Holden et al [44] reported that the incidence rate of major bleeding episodes in hemodialyzed patients was 2.5% per person-year and that use of aspirin and/or warfarin increased this risk. Based on the result of the meta-regression the mortality-rate of GI bleeding has improved since the 1980s. It is likely one of the reasons for the heterogeneity of the data. Inhomogen patient groups also result in a significant bias. However, the sensitivity analysis showed that none of the articles influences significantly the pooled OR.

Cardiovascular disease, current smoking [45] and even hemostasis disorders [46] may play a role in the background of higher risk for GI bleeding in ESRD patients. Unfortunately only a few of the analysed articles detailed the other comorbidities of the GI bleeding patients. In the article of Cheung et al [21], there was no significant difference in the comorbidities between ESRD, CKD and normal renal function group. More people in CKD and ESRD groups suffered from hypertension, diabetes mellitus and platelet abnormalities in the study of Sood et al [23], while the cirrhosis was less common than in controls. Volume replacement and blood transfusion are important parts of the therapy of GI bleeding. This meta-analysis demonstrated that patients with chronic impaired renal function develop 2.5 times more rebleeding episodes and require almost 2 more red blood cell units for transfusion than the control group. Patients with impaired renal function spent more time in the hospital than the control group.

There are several limitations to this study; therefore, the results of this meta-analysis should be regarded with caution. Unfortunately, only a low number of articles was found on this topic, with half of them written in the 1980s and 1990s. In the recent articles, CKD and ESRD groups were separated, but in the earlier publications these groups were mixed, leading to a bias in our analysis, and the definition of GFR was also not mentioned. The diagnosis was based on elevated creatinine level. Hung et al [37] only involved patients with cirrhosis and the mortality rate was monitored up to 6 wk, while hospital mortalities were presumably included in the other articles. Publications with rebleeding data did not follow patients for the same time interval, and 1 paper did not report on the follow-up time. The strength of this meta-analysis is the high number of patients.

Our results have demonstrated that patients with ESRD show higher mortality during GI bleeding. CKD patients require more transfusion, and the rebleeding rate is also more elevated than that in patients with normal renal function. Because of these severe conditions, the LOH is also longer. Patients with ESRD or CKD should be observed more carefully due to the elevated complication rate. In this meta-analysis, we wanted to highlight the importance of this clinical problem and we believe that it needs further scientific research. In order to understand the effect of CKD/ESRD and other comorbidities on the outcomes of GI bleeding in more details, observational trials, and registries on GI bleeding should be developed.

III. Disturbance of consciousness and acute pancreatitis

III.1 Introduction

III.1.1. Disturbance of consciousness

Patients hospitalized for AP may have a variety of neurological symptoms, such as confusion, alcohol withdrawal syndrome, and delirium. Disorder of consciousness (DOC) means the development of spatial and/or temporal disorientation, often occurring among hospitalized patients, especially the elderly. The (GCS) is a widespread point system for determining the state of consciousness. (Table 6).

Glasgow Coma Scale

Behavior	Response	Score
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1

Table 6. The Glasgow Coma Scale Scoring System.

Adding the scores of each answer gives the following evaluation results:

- GCS 8 or below - coma (unconscious)
- GCS 9-12 - moderate confusion
- GCS 13 or higher - slight confusion

Based on their depth and severity, we can distinguish between confusion, i.e., inability to think clearly, delirium, lethargy, and stupor. The disoriented patient is unable to assess his or her own relationship to the objects and locations around him or her and is not informed in time. Delirium means confused and illogical thinking, the delirious patient is often hallucinatory and disoriented. A patient with lethargy does not respond to external stimuli, even if it is a danger. Stupor is a deeper form of disturbance of consciousness, it can still respond to pain stimuli, but in its more severe form, the patient no longer responds to any external stimuli. Delirium is a nebulous, deeply overwhelmed state of consciousness characterized by severe visual, acoustic, and haptic sensory impairments, memory impairment, incoherent thinking, incoherent speech, intermittent aggression, agitation, dullness, behavioral abnormalities, sleep apnea, and wakefulness [47]. Delirium affects a third of hospitalized patients over 70 years of age. It can be triggered by relatively mild deterioration (constipation, sleep deprivation, exsiccosis, sensory depression, social isolation [48]. Other etiological factors may also induce delirium, such as organic, brain dysfunction, systemic disease (infection, hypoxia), metabolic abnormality or ionic disorder, toxic effect (alcohol, drug, or drug effect). An important subgroup of delirium is delirium tremens, which occurs in chronic ethyl consumers after acute 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. Alcoholism is a common condition that many clinicians have to contend with. Symptoms of alcohol withdrawal syndrome are caused by the depressant effects of alcohol on the central nervous system. Alcohol simultaneously increases inhibitory tone (by regulating GABA activity) and inhibits excitatory tone (by regulating excitatory amino acids). In the case of chronic alcohol consumption, homeostasis can be maintained only in the presence of alcohol for a longer time. As a result of abandoning chronic alcohol intake, we can see signs of central nervous system overactivity. Depending on

how much time elapsed after alcohol consumption, different phases of withdrawal can be observed [49] Table 7.

SYNDROME	CLINICAL SYMPTOMS	STARTING AFTER ALCOHOL WITHDRAWAL
SLIGHT WITHDRAWAL	Tremor, mild restlessness, headache, sweating, palpitations, anorexia, gastrointestinal symptoms, normal mental status.	6-36 hours
SPASM	Single or brief tonic-clonic seizures, short postictal period, status epilepticus rare.	6-48 hours
ALCOHOLIC HALLUCINOSIS	Visual, auditory and / or tactile hallucinations with intact orientation and normal vital parameters.	12-48 hours
DELIRIUM TREMENS	Delirium, agitation, tachycardia, hypertension, fever, sweating.	48-96 hours

(Table 7). Phases of alcohol withdrawal.

Risk factors for severe alcohol withdrawal syndrome include previous alcohol withdrawal events, delirium tremens, older age, concomitant surgical or internal medicine disease (trauma, infection, sepsis, liver failure, etc.), elevated blood alcohol levels, time of last drink consumption, previous benzodiazepine use, and male gender itself [50]. Mortality in delirium tremens is 5% but may be higher in the absence of treatment. Alcohol withdrawal syndrome and delirium tremens are often seen in patients with acute pancreatitis because alcohol is one of the leading etiologists of pancreatitis. Patients, who do not respond adequately to initial sedative doses, require close monitoring, and aggressive or even ICU therapy.

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 [51].

III.1.2. Clinical features

The pancreas is an abdominal, retroperitoneal organ that, plays various important and combined physiological roles. The insufficient exocrine or endocrine function can lead to numerous diseases, such as various types of diabetes mellitus, acute or chronic pancreatitis.
Acute pancreatitis (AP) is an inflammatory disease of the pancreas. The main symptoms are abdominal pain and elevated levels of pancreatic enzymes. Acute pancreatitis is one of the most common gastrointestinal diseases requiring urgent hospitalization worldwide, characterized by significant morbidity and mortality. The annual incidence of acute pancreatitis varies from country to country, averaging between 13 and 80 cases per 100,000 population. [52] The incidence is rising worldwide due to increased rates of obesity, alcohol consumption and gallstones. Depending on the severity of the disease mortality is still expected to be 2-5%. Mortality in AP is usually due to multi-organ failure in the first two-week period. After two weeks it is usually due to sepsis and its complications. The main etiological factors are biliary stones (40-70 %), alcohol (25-35 %) and hypertriglyceridemia (1-14 %). Also, several other minor factors may be included for example hypercalcemia, post-endoscopic retrograde cholangiopancreatography (ERCP), Genetic risk (*PRSS1, CFTR, SPINK1 gene mutation),* medications, biliary obstruction, autoimmune pancreatitis, infections and toxins. Besides, the cases are approximately 15-25% idiopathic. The definition of AP is based on the 2/3 rules. At least two of the following criteria must be present to diagnose AP [53, 54]: (1) clinical feature (upper abdominal pain), (2) laboratory measurement (serum amylase or lipase >3x upper limit of normal) (3) imaging (CT, MRI, ultrasonography) alterations such as edema or intraabdominal fluid.

III.1.3. Severity

The Revised Atlanta Classification (2012) divides acute pancreatitis into two main categories

- Interstitial edematous acute pancreatitis, which is characterized by acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis
- Necrotizing acute pancreatitis, which is characterized by inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis

Based on the severity, acute pancreatitis is divided into three groups:

- **Mild** acute pancreatitis which is characterized by the absence of organ failure and local or systemic complications
- **Moderate**ly severe acute pancreatitis which is characterized by transient organ failure (resolves within 48 hours) and/or local or systemic complications without persistent organ failure (>48 hours)
- **Severe** acute pancreatitis which is characterized by persistent organ failure that may involve one or multiple organs

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 [55]. In the case of moderate AP, organ failure develops and resolves within 48 h, while in severe forms, it persists longer [56] Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis. Organ failure is defined if two or more for any of three organ systems (respiratory, cardiovascular, or renal) is affected using the modified Marshall scoring system. A score of 2 or more over a period of more than 48 hours for any one of the three organ systems is defined as persistent organ failure while if it is present for less than 48 hours, is known as transient organ failure. Level of severity should be assessed during the disease process and hospital stay using this scoring system. Early and persistent organ failure is a strong indicator of increased mortality, and length of hospitalization. Persistent organ failure is widely accepted as a reliable criterion for severe AP [57]. Blood urea nitrogen is a predictive factor of persistent organ failure after 48h. There is no predictor

of persistent organ failure that can be justifiably used in clinical practice within 48h of admission [58].

III.1.4. Therapy and Risk assessment

Acute pancreatitis has no special therapy. We do not have special drugs that stop the inflammation. Therapy is mainly symptomatic and supportive. As a result of an adequate fluid treatment started in time, the formation of severe pancreatitis is less likely. In addition, supportive therapy includes adequate nutrition, analgesia, and, if necessary, antibiotic or interventional (endoscopic, radiological, surgical) therapy.

The ability to predict AP severity can help identify patients at increased risk for morbidity and mortality, thereby assisting in appropriate early triage to intensive care units and selection of patients for specific interventions. Multiple predictive models have been developed to predict the severity of AP based upon clinical, laboratory, and radiologic risk factors, various severity grading systems, and serum markers. Some of these can be performed on admission in the emergency room, while others can only be obtained after the first 48 to 72 hours. However, these predictive models have low specificity (ie, high false-positive rates), which, when coupled with the low prevalence of severe AP (15 to 25 percent), results in low positive predictive values. The most commonly used risk estimation point systems in the clinic are the APACHE II- and BISAP score. Both of these scoring systems include impaired mental status, the APACHE II score contains the GCS, while in the BISAP score the impaired mental status is present, but these systems evaluates it only on admission.

	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal temperature (°C)	≥41	39–40.9		38–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
MAP (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤40
Respiratory rate (/min)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
If FiO_2 ≥50%, check A-a gradient; if FiO_2 <50%, PaO_2									
A-a gradient	≥500	350–499	200–349		<200				
PaO_2 (mmHg)					>70	61–70		55–60	<55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.3–7.49		7.25–7.3	7.15–7.2	<7.15
Na (mM)	≥180	160–179	155–159	150–154	130–149		120–129	111–19	≤110
K (mM)	≥7	6–6.9		5–5.9	3.5–4.9	3–3.4	2.5–2.9		<2.5
Creatinine(mg/L)	≥35	20–34	15–19		6.0–14		<6.0		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count(10^9/L)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

Glasgow coma score (GCS): 0–12 points = 15–GCS

Age (y)	Points
<44	0
45–54	2
55–64	3
65–74	5
>75	6

Chronic health (history of chronic conditions)[a]	Points
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

Table 8. APACHE II scooring system[59]

Parameters	Score 0	Score 1
Blood urea nitrogen	<25 mg/dl	>25 mg/dl
Impaired mental status	Absent	Present
SIRS	Absent	Present
Age	<60 years	>60 years
Pleural effusion	Absent	Present

Table 9. The BISAP scooring system [60]

There are several risk factors worsening severity and mortality, but there is little knowledge of the factors that affect the outcome of the disease [5-9]. 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.

III.2. Hypotheses, objectives

Based on literature data, AP has several aggravating factors that worsen survival parameters. Of these factors predisposing to a negative outcome, we targeted disturbances of consciousness in our research because the literature in this area is incomplete.

Hypothesis 1.)

In case of development of disturbance of consciousness during hospitalization, the course of pancreatitis will be more severe, and LOH longer.

Hypothesis 2.)

The development of disturbance of consciousness is associated with more severe AP, thereby increasing the mortality of the underlying disease.

To verify our assumptions, we performed an analysis of HPSG prospective register data.

III.3 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 [53, 55, 61], 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. Table 12. 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. 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.

III.4. Results

III.4.1 General characteristics of the entire cohort

A total of 1220 cases from 20 centers were analyzed. The list of centers is shown in Table 10.

COUNTRY	TOWN	INSTITUTION	NO
Hungary	Pécs	First Department of internal Medicine, University of Pécs	362
	Szeged	First Department of Medicine, University of Szeged	200
		II. Hospital Szeged	47
		Second Department of Medicine, University of Szeged	36
		Emergency Unit, University of Szeged	10
		Department of Surgery, University of Szeged	4
	Székesfehérvár	Szent György University Teaching Hospital of County Fejér	199
	Budapest	Bajcsy-Zsilinszky Hospital	137
		Buda Hospital of the Hospitaller Order of Saint John of God	4
		Heim Pál Children's Hospital, Budapest, Hungary	1
	Debrecen	Department of Internal Medicine	76
		Institute of Surgery, University of Debrecen	7
	Békéscsaba	Dr. Réthy Pál Hospital	54
	Gyula	Pándy Kálmán Hospital of County Békés	26
	Miskolc	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	14
	Kecskemét	Bács-Kiskun County University Teaching Hospital	11
	Makó	Healtcare Center of County Csongrád	10
	Szentes	Dr. Bugyi István Hospital	10
	Szombathely	Markusovszky University Teaching Hospital	8
Romania	Targu Mures	Mures County Emergency Hospital	4
		Total number of patients	1220

Table 10. Distribution of patients by centers

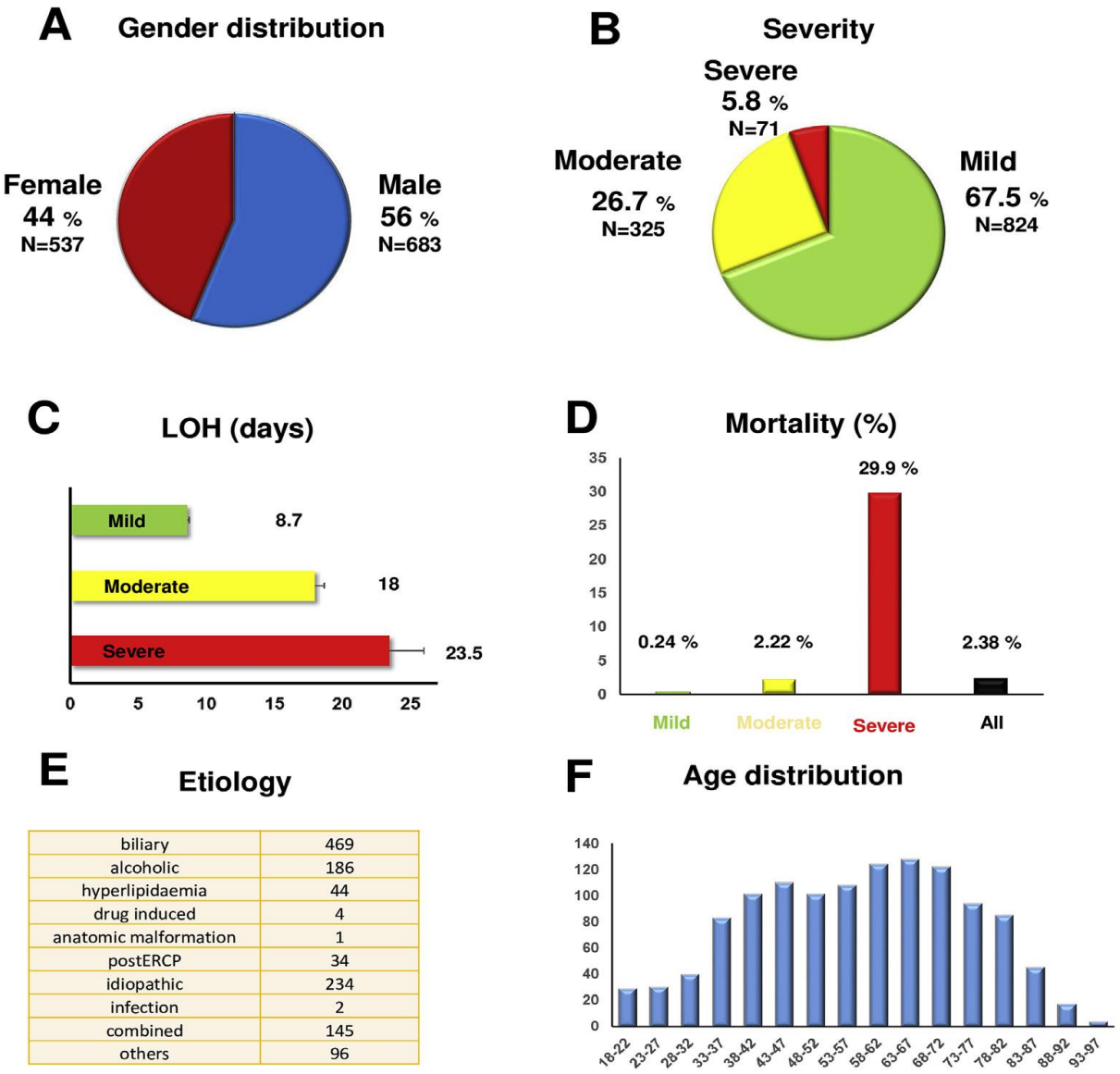
Data were complete for age, gender, etiology of pancreatitis, LOH, the severity of acute pancreatitis, and mortality. Our registry included data about alcohol consumption in 99.6% (Table 11).

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

Table 11. Data upload rate and accuracy

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

The basic characteristics of the analyzed population are shown in Fig. 11. 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 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. 11A-F).



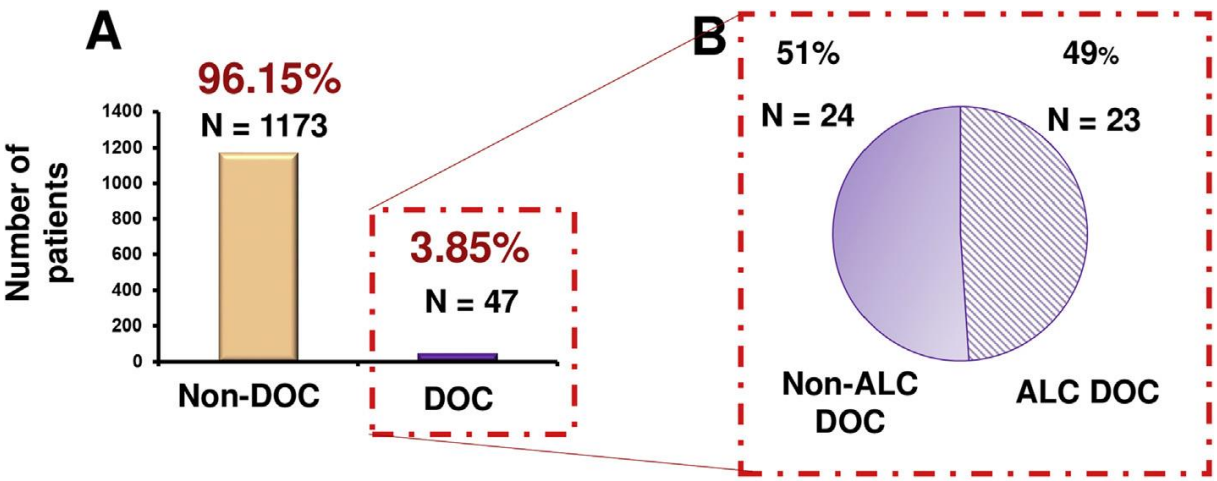
biliary	469
alcoholic	186
hyperlipidaemia	44
drug induced	4
anatomic malformation	1
postERCP	34
idiopathic	234
infection	2
combined	145
others	96

Fig. 11. A. Overall gender distribution. 11.B. Distribution based on severity. 11.C. The average length of hospitalization in days. 11.D. Overall mortality and mortality based on severity classes. 11.E. Distribution based on the etiology of acute pancreatitis. 11.F. Age distribution of the population.

III.4.2 Demographic characteristics in DOC vs. Non-DOC groups

From the 1220 patients of the HPSG registry, 47 patients (3.9%) developed DOC (Fig. 12A). 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. 12C).



C

Type of DOC

confusion	16
delirium	19
alcohol withdrawal	9
convulsion	3

Alcohol-related: 23

confusion	1
delirium	12
alcohol withdrawal	9
convulsion	1

Etiology

alcohol	23
sepsis	6
dementia	9
ischemia	3
idiopathic	4
hypoglycaemia	1
Impairment of salt and water balance	1

Non-alcohol related: 24

confusion	15
delirium	7
alcohol withdrawal	0
convulsion	2

Fig. 12. A Distribution of disturbance of consciousness (DOC) of patients with acute pancreatitis (n). 12.B Distribution of alcohol-related DOC (ALC DOC) and non-alcohol-related DOC (Non-ALC DOC) (n). 12.C Distribution of DOC based on type and etiology (n).

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 a higher incidence in men than in women (70.2% vs. 29.8%, n: 33 vs. n: 14, p: 0.045) (Fig. 13A). 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. 13C).

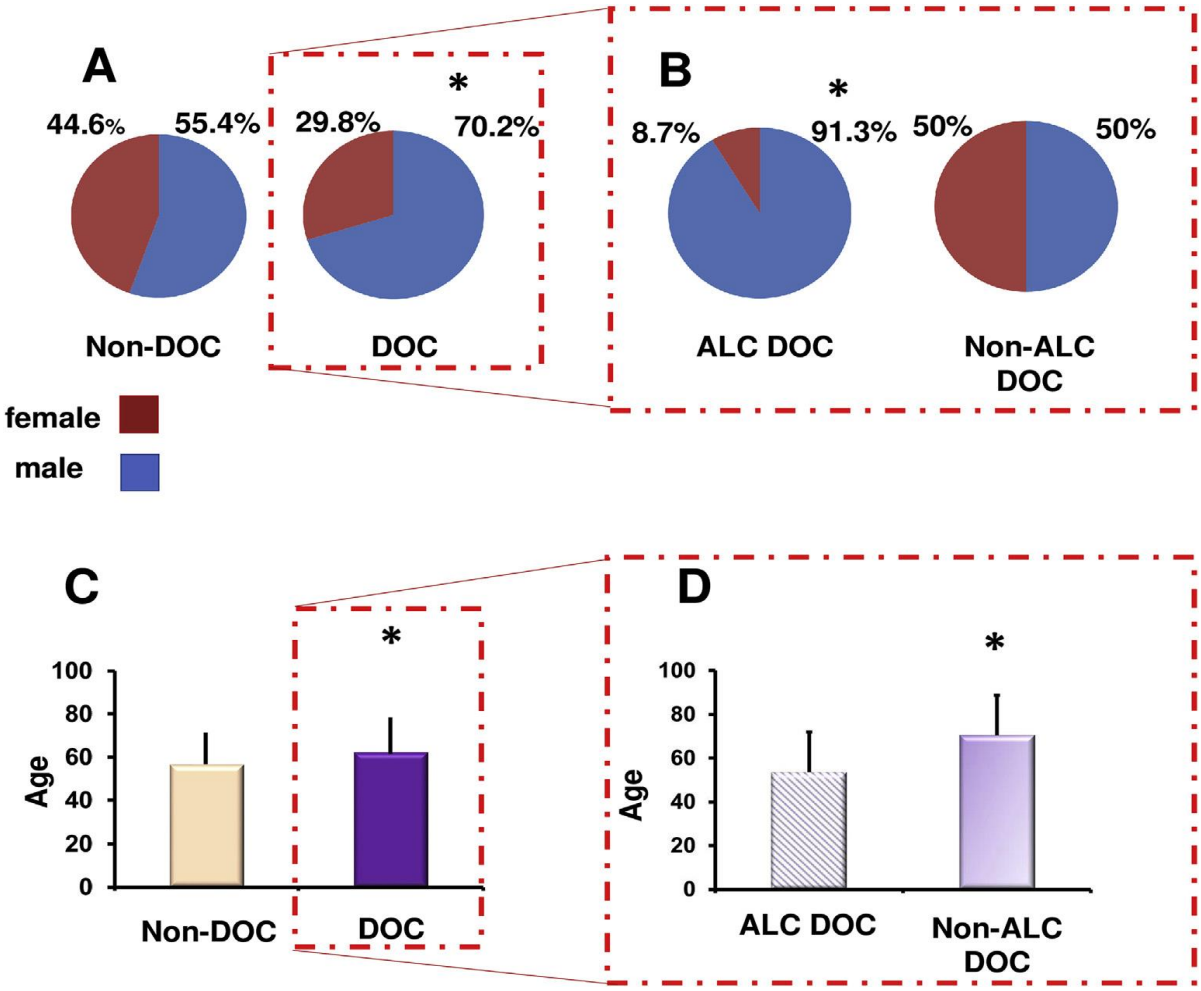


Fig. 13.A. Sex distribution of disturbance of consciousness (DOC) and Non-DOC groups (Compared with Chi-squared test). Fig. 13.B Sex distribution of alcohol-related DOC (ALC DOC) and non-alcohol-related (Non-ALC DOC) groups (Compared with Fisher-test). 13.C Age distribution of DOC and Non-DOC groups (Compared with independent sample t-test). 13.D. Age distribution of ALC DOC and Non-ALC DOC groups (Compared with independent sample t-test).

Table 12. 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.

Number of patients	Age	Gender	Type of DOC	Etiology of DOC	Time of onset	Number of episodes	Duration	Description of symptoms	Applied therapy
1	45	male	delirium	alcohol	N.A.	1	N.A.	delirium tremens	chlorpromazine, clonazepam
2	63	male	alcohol withdrawal	alcohol	1st day	1	2 days	agression, hyperactivity	clonazepam
3	67	male	alcohol withdrawal	alcohol	N.A.	1	N.A.	delirium tremens	N.A.
4	80	male	confusion	ischemia	1st day	1	2 weeks	confusion	N.A.
5	59	male	alcohol withdrawal	alcohol	1st day	1	N.A.	delirium tremens	clonazepam, tiapride
6	36	male	delirium	alcohol	N.A.	1	N.A.	delirium tremens	N.A.
7	84	male	delirium	alcohol	N.A.	1	N.A.	delirium tremens	N.A.
8	66	male	delirium	idiopathic	1st day	2	N.A.	delirium tremens	propofol, clonazepam
9	79	female	confusion	dementia	1st day	1	4 days	confusion	clonazepam, tiapride
10	65	male	delirium	alcohol	N.A.	2	N.A.	delirium tremens	clonazepam, haloperidol, dexmedetomidin, clonazepam, tiapride
11	87	female	confusion	idiopathic	7th day	1	N.A.	confusion	quetiapine
12	50	male	delirium	alcohol	1st day	1	1 days	delirium tremens	clonazepam
13	47	male	delirium	alcohol	1st day	1	N.A.	delirium tremens	N.A.
14	89	male	delirium	dementia	4th day	1	1 days	confusion	quetiapine
15	57	male	alcohol withdrawal	alcohol	1st day	1	N.A.	alcohol withdrawal	clonazepam
16	86	male	confusion	dementia	1st day	1	N.A.	confusion	tiapride
17	40	male	delirium	sepsis	1st day	1	N.A.	delirium	none
18	43	male	delirium	alcohol	1st day	1	3 days	delirium tremens	chlordiazepoxide
19	24	male	convulsion	idiopathic	N.A.	1	N.A.	convulsion	none
20	74	male	confusion	alcohol	1st day	1	4 days	confusion	risperdal
21	74	male	delirium	alcohol	8th day	1	3 days	delirium tremens	clonazepam, haloperidol
22	58	female	confusion	electrolyte imbalance	2 months	1	N.A.	hallucination	tiapride, alprazolam
23	70	male	alcohol withdrawal	alcohol	4th day	1	3 day	alcohol withdrawal	tiapride, clonazepam
24	83	female	confusion	dementia	N.A.	1	2 weeks	hyperactivity, confusion	tiapride, haloperidol
25	43	female	convulsion	alcohol	3rd day	1	minutes	convulsion	carbamazepine
26	92	male	confusion	ischemia	N.A.	1	N.A.	confusion	vinpocetine
27	90	female	confusion	hypoglycemia	1st day	1	N.A.	somnolence	glucose
28	74	female	confusion	idiopathic	5th day	1	N.A.	confusion	N.A.
29	68	male	delirium	sepsis	1st day	1	3 weeks	delirium tremens	venlafaxine

Number of patient	Age	Gender	Type of DOC	Etilogy of DOC	Time of onset	Number of episodes	Duration	Description of symptoms	Applied therapy
30	60	male	delirium	alcohol	1st day	1	N.A.	alcohol withdrawal	tiapride
31	44	male	delirium	alcohol	N.A.	1	N.A.	alcohol withdrawal	clonazepam, tiapride
32	54	male	alcohol withdrawal	alcohol	N.A.	1	N.A.	alcohol withdrawal	N.A.
33	61	male	alcohol withdrawal	alcohol	N.A.	1	N.A.	alcohol withdrawal	clonazepam
34	83	male	confusion	dementia	N.A.	1	N.A.	confusion	tiapride
35	43	male	delirium	sepsis	1st day	2	N.A.	delirium tremens, hallucination	dexmedetomidine, propofol, midazolam, risperidone
36	37	male	alcohol withdrawal	alcohol	1st day	1	N.A.	alcohol withdrawal syndrome	clonazepam, sertraline, tiapride
37	83	female	confusion	dementia	6th day	1	2 days	confusion	tiapride
38	72	male	confusion	dementia	10th day	1	N.A.	confusion	N.A.
39	35	male	delirium	alcohol	N.A.	1	N.A.	delirium tremens	propofol, midazolam, clonazepam, risperidone, haloperidol
40	48	female	delirium	sepsis	N.A.; 25th day	2	N.A.	agitatio, delirium	aplrazolam
41	47	male	delirium	sepsis	1st day	1	N.A.	delirium tremens	N.A.
42	33	male	delirium	alcohol	3rd day	1	10 days	delirium tremens, hyperactivity, agitation	tiapride chlordiazepoxide
43	30	female	alcohol withdrawal	alcohol	1st day	1	N.A.	alcohol withdrawal syndrome	chlordiazepoxide, clomethiazole
44	81	female	confusion	dementia	2nd day	1	N.A.	confusion	none
45	75	female	confusion	dementia	3rd day	1	N.A.	confusion	tiapride clonazepam
46	62	female	confusion	sepsis	N.A.	1	N.A.	confusion	N.A.
47	82	female	convulsion	ischemia	on admission	1	N.A.	convulsion	vinpocetine piracetam

Table 12. Data of disturbance of consciousness (DOC) of the 47 analyzed patients: time of onset, number of episodes, duration of DOC, description of symptoms, and applied therapy

III.4.3. 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. 12B). 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 group, the confusion with milder clinical features was more often present (n: 15) (Fig. 12C).
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. 13D).

III.4.4. 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. 14A), 8.8 times higher mortality (14.9% vs.1.7%, n: 7/ 47 vs. n: 20/1173, $p < 0.001$) (Fig. 14C), 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. 14E) respectively.

III.4.5. Severity and mortality of AP and LOH in ALC DOC vs. Non-ALC DOC groups

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. 14D). 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. 14F).

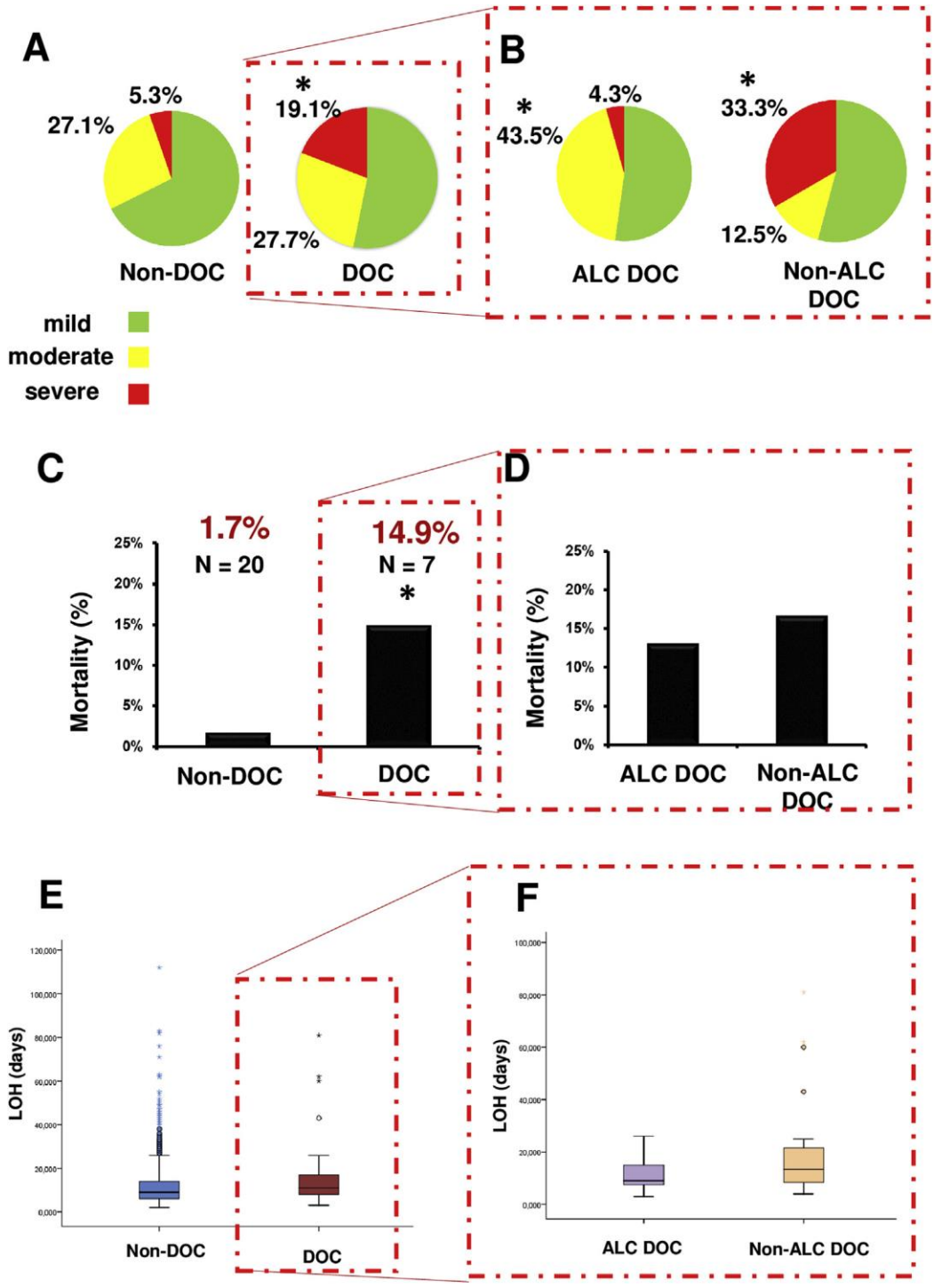


Fig. 14. A Distribution of severity of pancreatitis in disturbance of consciousness (DOC) and Non-DOC groups (Compared with Fisher test). 4.B Distribution of severity of acute pancreatitis of alcohol-related DOC (ALC DOC) and non-alcohol-related (Non-ALC DOC) groups (Compared with Fisher test). 4.C Distribution 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).

III.5 Discussion

The whole medical staff, especially nurses have an essential role in recognizing the early signs of changes in mental status and in preventing delirium [62]. However, the hospital-acquired delirium often remains unnoticed, because its symptoms resemble dementia and depression, further complicating the diagnosis [63]. 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 ICU, and it is also associated with longer ICU-stay [64]. 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 [65]. Furthermore, we found that moderate pancreatitis is more common in the ALC DOC group, whereas in the Non-ALC DOC 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.

A meta-analysis of randomized controlled studies suggests that dexmedetomidine could be a therapeutic option [66]. 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 [67]. 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 [68]. 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 [69]. 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 [70]. 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.

IV. Conclusions

This Ph.D work deals with the outcomes of two major GI disease, with GI bleeding and acute pancreatitis. In these life-threatening diseases a proper risk assessment is needed to detect the potential instabile and vulnerable patients.

According GI bleeding, there are several risk assessment and outcome predictor scoring systems which calculates outcome based on comorbidities, however, e.g. in terms of renal failure, the stages are not properly defined. Our work is the first meta-analysis and systematic review in this topic, which quantifies CKD as a negative risk factor in GI bleeding. GI bleeding in patients with chronic renal failure significantly increases the mortality rate, rebleeding rate, LOH, and they require more blood transfusion compared to patients with normal kidney functions. Kidney disease significantly worsens the outlook of patients presenting with GI bleeding. Patients with CKD will need to be treated with more caution due to the worse outcomes of GI bleeding. Although CKD, ESRD, and other comorbidities are major risk factors for unfavorable outcomes in GI bleeding, their roles are not well investigated nor understood and they need further scrutiny. We would better understand the role of CKD in ESRD in GI bleeding from analysis of extensive data from large multicenter and multinational observational studies and registries accurately recording the outcomes and the kidney functions.[71]

Acute pancreatitis is one of the most common gastrointestinal diseases requiring urgent hospitalization worldwide, characterized by significant morbidity and mortality. Several scoring systems are available, but they characterize patients on admission. Disorder of consciousness may develop in severe diseases, also in AP, but there is no literature about the influence of DOC on the outcome of AP. This is the first cohort analysis from the HPSG registry data, which showed that DOC is associated with a more severe course of AP, these patients requires longer LOH. In these patients a higher mortality rate of the underlying disease. Alcohol consumption in medical history elevates the rate of moderate AP in the DOC group. 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.[72]

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VI. References

1. Laura E. Targownik, A.N., *Trends in Management and Outcomes of Acute Nonvariceal Upper Gastrointestinal Bleeding: 1993–2003.* Clinical Gastroenterology and Hepatology, 2006: p. 1459 –1466.
2. Rockall, T.A., et al., *Risk assessment after acute upper gastrointestinal haemorrhage.* Gut, 1996. **38**(3): p. 316-21.
3. Demcsák, A., et al., *Acid suppression therapy, gastrointestinal bleeding and infection in acute pancreatitis - An international cohort study.* Pancreatology, 2020.
4. Farkas, N., et al., *A Multicenter, International Cohort Analysis of 1435 Cases to Support Clinical Trial Design in Acute Pancreatitis.* Frontiers in Physiology, 2019. **10**(1092).
5. Mosztbacher, D., et al., *Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases.* Pancreatology, 2020. **20**(4): p. 608-616.
6. Kiss, L., et al., *The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis.* Scientific Reports, 2018. **8**(1): p. 14096.
7. Whitcomb, D.C., *Clinical practice. Acute pancreatitis.* The New England Journal of Medicine, 2006. **354**(20): p. 2142-50.
8. Párniczky, A., et al., *Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations.* Pancreatology, 2019. **19**(4): p. 488-499.
9. Marshall, J.C., et al., *Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.* Critical Care Medicine, 1995. **23**(10): p. 1638-52.
10. Cutler, J.A. and A.I. Mendeloff, *Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S.* Digestive Diseases and Sciences, 1981. **26**(7 Suppl): p. 90s-96s.
11. Vreeburg, E.M., et al., *Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome.* The American Journal of Gastroenterology, 1997. **92**(2): p. 236-43.

12. Rob P. Adang, R.W.S., *Appropriateness of indications for diagnostic upper gastrointestinal endoscopy: Association with relevant endoscopic disease.* Gastrointestinal Endoscopy, 1995. **42**(5): p. 390-397.
13. Hussain, H., S. Lapin, and M.S. Cappell, C*linical scoring systems for determining the prognosis of gastrointestinal bleeding.* Gastroenterology Clinics of North America, 2000. **29**(2): p. 445-464.
14. Zuccaro, G., Jr., *Management of the adult patient with acute lower gastrointestinal bleeding. American College of Gastroenterology. Practice Parameters Committee.* The American Journal of Gastroenterology, 1998. **93**(8): p. 1202-8.
15. Lin, C.C., et al., *The etiology and clinical characteristics of acute lower gastrointestinal bleeding in patients hospitalized for comorbid illnesses.* Hepatogastroenterology, 2006. **53**(69): p. 395-8.
16. Laeeq Syed, M., et al., *Upper gastrointestinal bleeding in patients with end stage renal disease: causes, characteristics and factors associated with need for endoscopic therapeutic intervention.* Journal of Translational Internal Medicine. 2017. p. 106.
17. Blatchford o, M.W.R., Blatchford M, *A risk score to predict need for treatment for upper-gastrointestinal haemorrhage.* Lancet, 2000: p. 1318-21.
18. Saltzman R., T.P.H.H., Johannes S., *A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding.* Gastrointestinal Endoscopy, 2011. **74**(6): p. 1215-1224.
19. Mankongpaisarnrung, C., et al., *Risk assessment in patients with gastrointestinal bleeding.* The Southwest Respiratory and Critical Care Chronicles, 2013. **1**: p. 15.
20. Stevens, L.A., et al., *Assessing kidney function-measured and estimated glomerular filtration rate.* The New England Journal of Medicine, 2006. **354**(23): p. 2473-83.
21. Cheung, J., et al., *Peptic ulcer bleeding outcomes adversely affected by end-stage renal disease.* Gastrointestinal Endoscopy, 2010. **71**(1): p. 44-9.
22. Kuo, C.C., et al., *The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a population-based cohort study.* BMC Nephrology, 2013. **14**: p. 15.
23. Sood, P., et al., *Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding.* American Journal of Nephrolgy, 2012. **35**(3): p. 216-24.
24. Gheissari, A., et al., *Gastrointestinal hemorrhage in end stage renal disease patients.* International Surgery, 1990. **75**(2): p. 93-5.

25. Docherty, E., et al., *Use of small bowel capsule endoscopy in patients with chronic kidney disease: experience from a University Referral Center.* Annals of Gastroenterology, 2015. **28**(1): p. 99-104.
26. Karagiannis, S., et al., *Wireless capsule endoscopy in the investigation of patients with chronic renal failure and obscure gastrointestinal bleeding (preliminary data).* World Journal of Gastroenterology, 2006. **12**(32): p. 5182-5185.
27. Ohmori, T., et al., *Abnormalities of the small intestine detected by capsule endoscopy in hemodialysis patients.* Internal Medicine, 2012. **51**(12): p. 1455-60.
28. Matera James J., M.J., *Diet Planning Guide: Nutritional Considerations in CKD and ESRD.* Nutrition 411, 2019.
29. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS Medicine, 2009. **6**(7): p. e1000097.
30. Tsai, C.J. and J.C. Hwang, *Investigation of upper gastrointestinal hemorrhage in chronic renal failure.* Journal of Clinical Gastroenterology, 1996. **22**(1): p. 2-5.
31. Boyle, J.M. and B. Johnston, *Acute upper gastrointestinal hemorrhage in patients with chronic renal disease.* The American Journal of Medicine, 1983. **75**(3): p. 409-12.
32. Hozo, S.P., B. Djulbegovic, and I. Hozo, *Estimating the mean and variance from the median, range, and the size of a sample.* BMC Medical Research Methodology, 2005. **5**: p. 13.
33. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011.
34. Wells, G., et al., *The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis*, 2000.
35. Stevens, P.E. and A. Levin, *Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline.* Annals of Internal Medicine, 2013. **158**(11): p. 825-30.
36. Alvarez, L., J. Puleo, and J.A. Balint, *Investigation of gastrointestinal bleeding in patients with end stage renal disease.* The American Journal of Gastroenterology, 1993. **88**(1): p. 30-3.
37. Hung, T.H., et al., *Is end stage renal disease a risk factor for the mortality of cirrhotic patients with esophageal variceal bleeding?* Hepatogastroenterology, 2014. **61**(135): p. 1871-5.

38. Zuckerman, G.R., et al., *Upper gastrointestinal bleeding in patients with chronic renal failure.* Annals of Internal Medicine, 1985. **102**(5): p. 588-92.
39. Khedmat, H., et al., *Gastro-duodenal lesions and Helicobacter pylori infection in uremic patients and renal transplant recipients.* Transplantation Proceedings, 2007. **39**(4): p. 1003-7.
40. Sugimoto, M., et al., *Prevalence of Helicobacter pylori infection in long-term hemodialysis patients.* Kidney International, 2009. **75**(1): p. 96-103.
41. Luo, J.C., et al., *Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis.* CMAJ, 2011. **183**(18): p. E1345-51.
42. Kalman, R.S. and M.C. Pedrosa, *Evidence-based review of gastrointestinal bleeding in the chronic kidney disease patient.* Seminars is Dialysis, 2015. **28**(1): p. 68-74.
43. Weng, S.C., et al., *In-hospital mortality risk estimation in patients with acute nonvariceal upper gastrointestinal bleeding undergoing hemodialysis: a retrospective cohort study.* Renal Failure, 2013. **35**(2): p. 243-8.
44. Holden, R.M., et al., *Major bleeding in hemodialysis patients.* Clinical Journal of the American Society of Nephrology, 2008. **3**(1): p. 105-10.
45. Wasse, H., et al., *Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients.* Kidney International, 2003. **64**(4): p. 1455-61.
46. Jalal, D.I., M. Chonchol, and G. Targher, *Disorders of hemostasis associated with chronic kidney disease.* Seminars in Thrombosis and Hemostasis, 2010. **36**(1): p. 34-40.
47. Szirmai, I., *A tudat és a tudatzavarok, Medicina Könyvkiadó Zrt, XI. fejezet.* . 2011. 158–75.
48. Székely, M. 2013. Kórélettani alapok. Medicina Könyvkiadó Zrt. 7.5. fejezet: A pancreas működési zavarai, 238–40.; A11.2.3. Tudatborult állapotok, 492–93. .
49. Perry, E.C., *Inpatient management of acute alcohol withdrawal syndrome.* CNS Drugs, 2014. **28**(5): p. 401-10.
50. Carlson, R.W., et al., *Alcohol withdrawal syndrome.* Critical Care Clinics, 2012. **28**(4): p. 549-85.
51. Sun, G.H., et al., *Pancreatic encephalopathy and Wernicke encephalopathy in association with acute pancreatitis: a clinical study.* World Journal of Gastroenterology, 2006. **12**(26): p. 4224-7.
52. Yadav, D. and A.B. Lowenfels, *The epidemiology of pancreatitis and pancreatic cancer.* Gastroenterology, 2013. **144**(6): p. 1252-1261.

53. Szakacs, Z., et al., *Aging and Comorbidities in Acute Pancreatitis II.: A Cohort-Analysis of 1203 Prospectively Collected Cases.* Frontiers in Physiology, 2018. **9**: p. 1776.

54. Szentesi, A., et al., *Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects.* Frontiers is Physiology, 2019. **10**: p. 1202.

55. Parniczky, A., et al., *Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis.* PLoS One, 2016. **11**(10): p. e0165309.

56. Banks, P.A., et al., *Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus.* Gut, 2013. **62**(1): p. 102-11.

57. Buter, A., et al., *Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis.* British Journal of Surgery, 2002. **89**(3): p. 298-302.

58. Yang, C.J., et al., *Predictors of severe and critical acute pancreatitis: a systematic review.* Digestie and Liver Disease, 2014. **46**(5): p. 446-51.

59. Lee, W.-S., J.-F. Huang, and W.-L. Chuang, *Outcome assessment in acute pancreatitis patients.* The Kaohsiung Journal of Medical Sciences, 2013. **29**: p. 469-77.

60. Kantly, R. and A. Medikeri, *Study on severity assessment of acute pancreatitis using BISAP score in rural area of south India.* International Surgery Journal, 2018.

61. Miko, A., et al., *Preexisting Diabetes Elevates Risk of Local and Systemic Complications in Acute Pancreatitis: Systematic Review and Meta-analysis.* Pancreas, 2018. **47**(8): p. 917-923.

62. Faught, D.D., *Delirium: The Nurse's Role in Prevention, Diagnosis, and Treatment.* Medsurg Nursing, 2014. **23**(5): p. 301-5.

63. Volland, J., A. Fisher, and D. Drexler, *Preventing and identifying hospital-acquired delirium.* Nursing, 2020. **50**(1): p. 32-37.

64. Lahariya, S., et al., *Delirium in patients admitted to a cardiac intensive care unit with cardiac emergencies in a developing country: incidence, prevalence, risk factor and outcome.* General Hospital Psychiatry, 2014. **36**(2): p. 156-64.

65. Trogrlic, Z., et al., *A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes.* Critical Care, 2015. **19**: p. 157.

66. Pasin, L., et al., *Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials.* Journal of Cardiothorac and Vascular Anesthesia, 2014. **28**(6): p. 1459-66.

67. D'Onofrio, G., et al., *Lorazepam for the prevention of recurrent seizures related to alcohol.* The New England Journal of Medicine, 1999. **340**(12): p. 915-9.
68. Gershkovich, P., et al., *Effect of variations in treatment regimen and liver cirrhosis on exposure to benzodiazepines during treatment of alcohol withdrawal syndrome.* Drugs Context, 2015. **4**: p. 212287.
69. Garpestad, E. and J.W. Devlin, *Polypharmacy and Delirium in Critically Ill Older Adults: Recognition and Prevention.* Clinincs in Geriatric Medicine, 2017. **33**(2): p. 189-203.
70. Godfrey, M., et al., *Process of implementing and delivering the Prevention of Delirium system of care: a mixed method preliminary study.* BMC Geriatrics, 2019. **20**(1): p. 1.
71. Hágendorn, R., et al., *Chronic kidney disease severely deteriorates the outcome of gastrointestinal bleeding: A meta-analysis.* World Journal of Gastroenterology, 2017. **23**(47): p. 8415-8425.
72. Hágendorn, R., et al., *Development of disturbance of consciousness is associated with increased severity in acute pancreatitis.* Pancreatology, 2020. **20**(5): p. 806-812.

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META-ANALYSIS

Chronic kidney disease severely deteriorates the outcome of gastrointestinal bleeding: A meta-analysis

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Abstract

AIM

To understand the influence of chronic kidney disease (CKD) on mortality, need for transfusion and rebleeding in gastrointestinal (GI) bleeding patients.

METHODS

A systematic search was conducted in three databases for studies on GI bleeding patients with CKD or end-stage renal disease (ESRD) with data on outcomes of mortality, transfusion requirement, rebleeding rate and length of hospitalization (LOH). Calculations were performed with Comprehensive Meta-Analysis software using the random effects model. Heterogeneity was tested by using Cochrane's Q and I^2 statistics. Mean difference (MD) and OR (odds ratio) were calculated.

RESULTS

1063 articles (EMBASE: 589; PubMed: 459; Cochrane: 15) were found in total. 5 retrospective articles and 1 prospective study were available for analysis. These 6 articles contained data on 406035 patients, of whom 51315 had impaired renal function. The analysis showed a higher mortality in the CKD group (OR = 1.786, 95%CI: 1.689-1.888, $P < 0.001$) and the ESRD group (OR = 2.530, 95%CI: 1.386-4.616, $P = 0.002$), and a rebleeding rate (OR = 2.510, 95%CI: 1.521-4.144, $P < 0.001$) in patients with impaired renal function. CKD patients required more unit red blood cell transfusion (MD = 1.863, 95%CI: 0.812-2.915, $P < 0.001$) and spent more time in hospital (MD = 13.245, 95%CI: 6.886-19.623, $P < 0.001$) than the controls.

CONCLUSION

ESRD increases mortality, need for transfusion, rebleeding rate and LOH among GI bleeding patients. Prospective patient registries and observational clinical trials are crucially needed.

Key words: Gastrointestinal bleeding; Chronic kidney disease; Mortality; Blood transfusion; Rebleeding

Core tip: Acute gastrointestinal bleeding is a potentially life-threatening abdominal emergency that remains a common cause of hospitalization. Pre-existing chronic kidney disease (CKD) may worsen the prognosis. This is the first meta-analysis to compare CKD patients and normal renal function patients based on GI bleeding. We investigated these two groups in terms of mortality, transfusion amount, rebleeding rate and length of hospitalization.

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INTRODUCTION

Acute gastrointestinal bleeding (GI) is an abdominal emergency which remains a common cause of hospitalization[1]. An accurate diagnosis of GI bleeding relies on prompt resuscitation, initial risk evaluation, and provisional clinical diagnosis followed by an appropriate definitive investigation which enables specific therapeutic interventions. GI bleeding involves any bleeding in the GI tract from the esophagus, stomach, small intestines or large intestines to the anus.

Upper GI bleeding has an annual incidence that ranges from 40 to 150 episodes per 100000 persons and a morality rate of 6%-10%[2], whereas lower GI bleeding has an annual incidence ranging from 20 to 27 episodes per 100000 persons and a mortality rate of 4%-10%[3,4]. Since GI bleeding is a potentially life-threatening acute disorder, understanding the risk factors that worsen the disease is of great importance. Scoring systems have therefore been developed to predict the outcome of therapy. The Rockall score is one of these scoring systems. It includes pre-endoscopic (age, shock and comorbidity) and post-endoscopic (diagnosis and presence or absence of endoscopic stigmata of recent haemorrhage) factors[5]. Several studies have demonstrated high mortality with higher Rockall scores[6]. However, Laeeq *et al*[7] have not found significantly higher mortality in patients with high pre-endoscopic Rockall score (> 5). The Rockall score only assesses the risk of mortality in patients with upper GI bleeding. The Glasgow Blatchford score is another scoring system which uses clinical and laboratory parameters. Neither scoring system makes distinction between pre-existing renal failure and acute renal failure due to haemorrhage. Both of these scoring systems have been designed for the risk assessment of upper GI bleeding. Previous studies have shown evidence of increased risk of GI bleeding in chronic kidney disease (CKD) patients and with end-stage renal disease (ESRD) requiring renal replacement therapy in comparison with the general population, but also an association with higher

mortality[8-10]. Further studies have demonstrated that bleeding in CKD patients from the upper GI tract is more common than from the lower GI tract[11]. The increased prevalence of small bowel erosions, ulcers and angioectasias is also well known in CKD patients and it may be as high as 33% and it often causes obscure gastrointestinal bleeding[12-14]. However, no meta-analyses or systematic reviews have been conducted to assess the difference between CKD/ESRD patients and the normal renal function population with regard to GI bleeding.

The aim of this study was therefore to examine outcomes of GI bleeding, such as mortality, blood transfusion requirement, rebleeding rate and length of hospitalization (LOH) in CKD/ESRD patients compared to patients with normal renal functions.

MATERIALS AND METHODS

Search strategy

This study was conducted using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)[15]. It was registered in the international prospective register of systematic reviews, PROSPERO (under registration number CRD42017077987). The meta-analysis was based on the PICO (Patient, Intervention, Comparison, Outcome) format (P: patients with GI bleeding; I: chronic renal failure; C: normal renal function; O: mortality, blood transfusion, rebleeding). A systematic search was performed in 3 databases, Pubmed, EMBASE and the Cochrane Library, with the following terms: ("GI bleeding" OR "gastrointestinal bleeding" OR "gastrointestinal hemorrhage") AND ("chronic renal failure" OR "uremia" OR "chronic kidney failure"). The search was limited to human data and to full-text English-language articles if appropriate. The exact search term in Pubmed was: ["GI bleeding" (All Fields) OR "gastrointestinal bleeding"(All Fields) OR "gastrointestinal hemorrhage"(All Fields)] AND ["chronic renal failure"(All Fields) OR "uraemia" (All Fields) OR "uremia"(MeSH Terms) OR "uremia" (All Fields) OR "chronic kidney failure"(All Fields)] AND ["humans"(MeSH Terms) AND English(lang)]. The database search was conducted up to 10 March 2017. Reference management software (EndNote X7) was used to remove duplicates by searching overlaps between titles, authors and publication years. The reference lists in the articles obtained were also checked, and one more eligible publication was found.

Study selection

The studies were selected separately by two investigators (RH and AM). Disagreements were resolved by consulting a third reviewer (PH). Clinical studies were eligible provided they reported data on adult patients hospitalized with upper or lower GI bleeding grouped into normal renal function and CKD or ESRD groups. Articles were eligible containing data of CKD/ESRD patients and a control group in the same study. Information on mortality, transfusion, rebleeding and length of hospitalization (LOH) was manually searched. Case reports, conference abstracts, reviews and studies on paediatric patients up to age 18 alone were excluded. We found a high number of articles in which the risk of GI bleeding in CKD patients was studied, but they were not eligible for our meta-analysis, as there were no data available on outcomes of the GI bleeding in a control population without CKD/ESRD.

Data extraction, synthesis and analysis

Mortality data, number of transfused blood units, rebleeding and length of hospitalization data were extracted to analyse the influence of CKD and/or ESRD on the outcome of GI bleeding. In Sood *et al*[9], Tsai *et al*[16] and Boyle *et al*[17], the number of patients was calculated from percentages of mortality. Boyle *et al*[17] supplied information on transfusion in mean and standard error of mean, for which statistical calculation standard deviation (SD) was computed. Tsai *et al*[16] reported data from transfusions in the median and interquartile range (IQR), from which mean and SD were calculated with Hozo's method[18]. All meta-analytic calculations were performed with Comprehensive Meta-Analysis software (Version 3.0, Biostat Inc.) using the random effects model (DerSimonian-Laird method[19]). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for binary outcomes. In the case of LOH and transfusion for comparing mean data, a mean difference (MD) with 95%CI was calculated. All analyses were two-tailed, with an α of 0.05.

Heterogeneity was tested using Cochrane's Q and the I^2 statistics. Based on the Cochrane Handbook, $I^2 = 100\% \times (Q - df)/Q$, with I^2 representing the magnitude of the heterogeneity (moderate: 30%-60%; substantial: 50%-90%; considerable: 75%-100%)[20]. Only results that were available from at least 3 studies were displayed graphically with forest plots. We performed a sensitivity analysis to assess whether removing any study result in different interpretation and final conclusion[21]. To assess the effect of the year of publication on the outcome data we performed meta-regression analysis. We calculated the regression coefficient and interpreted the data with their 95%CI and r-analog.

Quality of studies and risk of bias

Because of the low number of eligible articles, publication bias was obtained with a visual inspection of the funnel plots alone according to the Cochrane Handbook[20]. The Newcastle-Ottawa Scale (NOS) adjusted to our study design was used[22] to assess the quality of nonrandomized cohort studies. The

Table 1 Modified Newcastle-Ottawa Scale criteria

Adapted Newcastle-Ottawa Scale Items	High-quality items carrying a low risk of bias (green)	Low-quality items carrying a high (red) or an unknown (yellow) risk of bias
Item 1: Representativeness of the initial study population - patients with GI bleeding and CKD/ESRD	All patients with upper or lower GI bleeding and CKD/ESRD were included.	Low: any selection criteria were applied to the study population (*e.g.*, only transplanted patients). Unknown: no data on selection process.
Item 2: Representativeness of the initial study population - patients with GI bleeding without CKD/ESRD	All patients with upper or lower GI bleeding without CKD/ESRD included.	Low: any selection criteria were applied to the study population. Unknown: no data on selection process.
Item 3: Ascertainment of exposure	We defined chronic renal failure as present when eGFR was < 60 mL/min at least 3 mo. We defined end-stage renal disease as a condition where hemodialysis or chronic peritoneal dialysis is performed at least for 3 mo.	Low: CKD or ESRD is not present in all of the patients. Unknown: no definitions of the conditions mentioned are provided.
Item 4: Comparability of cohorts A	Study controls for age: no significant difference was detected.	Low: significant difference was detected. Unknown: no statement.
Item 5: Comparability of cohorts B	Study controls for taking ulcerogenic drugs: no significant difference was detected	Low: significant difference was detected between taking ulcerogenic drugs. Unknown: no comparison made by taking ulcerogenic drugs.
Item 6: Follow-up time for rebleeding	The follow-up time is clearly defined.	Low: incomplete follow-up Unknown: no follow-up time is mentioned.

CKD: Chronic kidney disease; ESRD: End-stage renal disease.

selection, comparability and outcome data were assessed based on 6 items (Table 1) with the "star system": high-quality items with a low risk of bias received one star, while low-quality items with a high or unknown risk of bias were assigned no stars. 3 items were included during the selection process. In the case of representativeness in the study population, we assigned a star if all of the GI bleeding patients with normal or impaired renal function were included. If any selection criteria applied, we assigned no points. We used the classical definition of CKD[23], which characterizes the disease with a glomerular filtration rate (GFR) < 60 m/min lasting longer than 3 mo. ESRD was defined as a condition where haemodialysis or chronic peritoneal dialysis is performed for at least 3 mo. With regard to outcome, only the follow-up time for rebleeding was rated in articles that provided this information. Assessment of outcome and length of follow-up were not rated because most of the articles were retrospective.

RESULTS

Study selection

1063 articles (EMBASE: 589; PubMed: 459; Cochrane: 15) were found altogether through database searches. The flowchart (Figure 1) shows the study selection strategy. Studies in our meta-analysis were dated from 1946 to 2017. After removing duplicates, 875 publications remained. Following initial screening based on titles and abstracts, 23 articles were retrieved and screened. A further 18 were excluded because of missing outcome data or a missing control group. Patients with acute renal failure were also included in the analysis reported in Alvarez *et al*[24], so we did not use the data in that publication. The remaining 5[9,16,17,25,26] and one other[10] eligible record which was found in reference lists were included in the meta-analysis. The basic characteristics of the 6 eligible articles in the meta-analysis are shown in Table 2. These 6 publications contained data on 406,035 patients, of whom 51315 had impaired renal function parameters and 354720 had normal renal functions. 2 articles contained data on patients with CKD and 4 on ESRD patients. There were 2 studies involving CKD and ESRD patients, with their group identified as the CKD mixed group. The number of ESRD patients analysed was 15201, the CKD group had 36035 members, and 79 patients could be classified in the CKD mixed group.

Mortality

Data on mortality was available in all of the articles included, but Zuckerman *et al*[26] reported no mortality data for the control group; we therefore removed it from the statistical analysis. Hung *et al*[25] reported mortality data from a 6-wk follow-up period, while the other articles contained data on an unknown follow-up period. In the subgroup analysis for CKD and ESRD, a higher mortality rate was detected compared to the control population (CKD: OR = 1.786, 95%CI: 1.689-1.888, $P < 0.001$; ESRD: OR = 2.530, 95%CI: 1.386-4.616, $P = 0.002$, Figure 2).

Required units for transfusion

4 studies reported data on the transfused units of red blood cells. The required transfusion was 1.8 times higher in the patients with abnormal renal function (MD

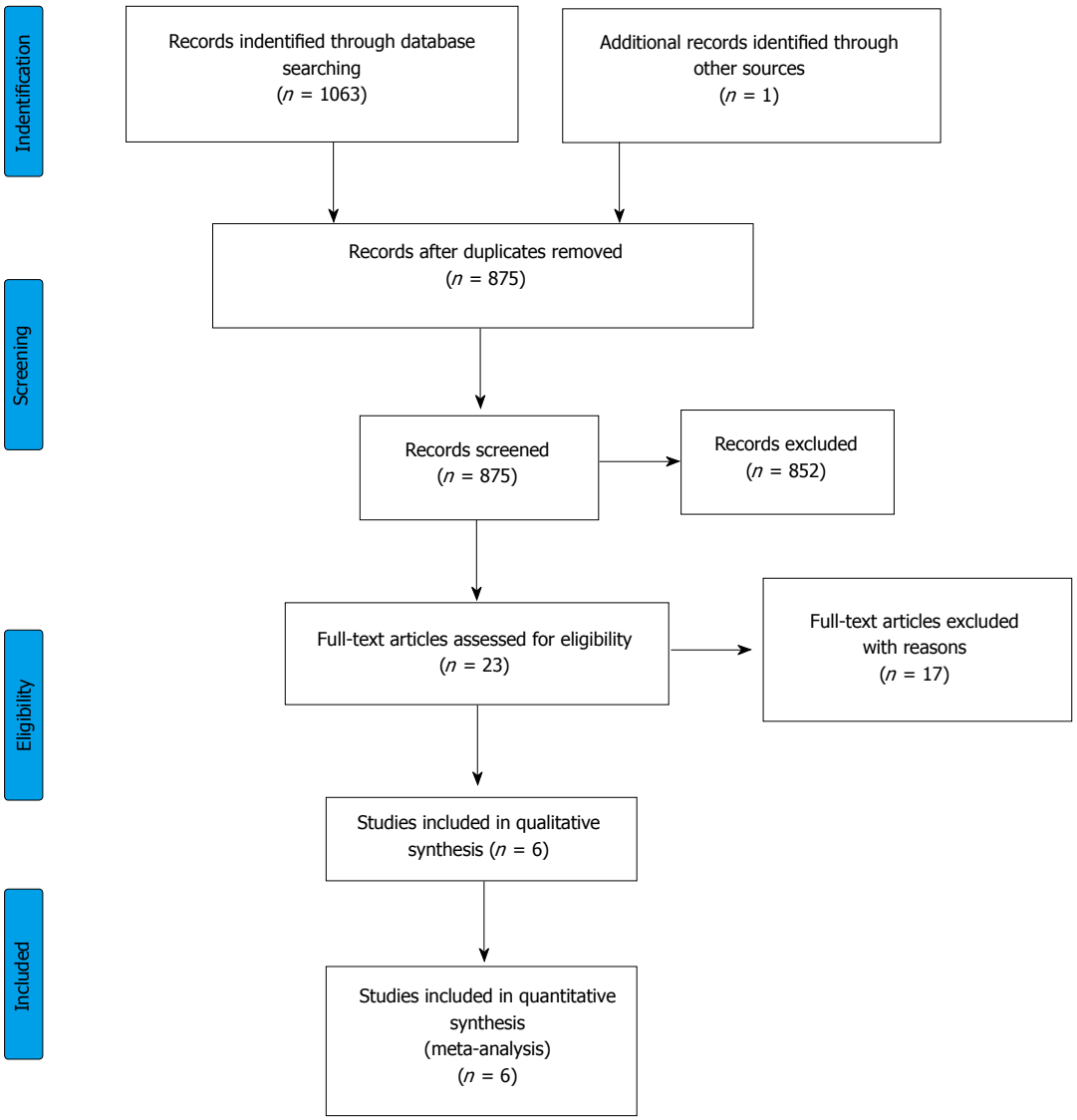

Figure 1 Flowchart of the study selection procedure.

= 1.863, 95%CI: 0.812-2.915, $P < 0.001$, Figure 3).

Rebleeding rate

It was possible to retrieve data on the rebleeding rate from 3 articles, but Cheung *et al*[10] contained simultaneous data from the CKD and ESDR groups, which could be analysed. Boyle *et al*[17]. also presented data on rebleeding. However, this included cases of uncontrolled bleeding, so we excluded these data from our analysis. We found that patients with impaired renal function tend to bleed again 2.5 more times than patients with normal renal function (OR = 2.510, 95%CI: 1.521-4.144, $P < 0.001$, Figure 4).

Length of hospitalization

Two of the six articles included reported hospital stay outcomes. Patients with impaired renal function spent significantly more time in hospital after GI bleeding (MD = 13.245, 95%CI: 6.886-19.623, $P < 0.001$, Figure 5).

Heterogeneity and quality assessment of data

High heterogeneity was detected for mortality in the ESRD group (Q = 17.082; DF = 3; $I^2 = 82.438\%$; $P < 0.001$), while the heterogeneity for CKD was low (Q = 1.767; DF = 2; $I^2 = 0\%$; $P = 0.413$). However, a low heterogeneity was detected for the transfusion requirements (Q = 3.448; DF = 3; $I^2 = 13.003\%$; $P = 0.328$), the rebleeding rate (Q = 3.328; DF = 3; $I^2 = 9.845\%$; $P = 0.344$) and LOH (Q = 1.100; DF = 2; $I^2 = 0\%$; $P = 0.577$). To ascertain publication bias, we only made a visual assessment of the funnel plot (Figure 6) because we were only able to include 6 studies in our meta-analysis. Sensitivity analysis showed no significant difference in the OR of mortality, by removing any of the articles (Supplementary Figure 1). Meta-regression showed slight significance, in the

Table 2 Basic characteristics of the studies included in the meta-analysis

Ref.	Country	Study type	Years of study	Group	Sample size	Age	Mortality	Transfusion	Rebleeding	Length of hospitalization
Boyle *et al*[17], 1983	United States	Retrospective	1977-1981	Control	40	54 ± 2[1]	√	√	-	√
				CKD (mix)	20	59 ± 4[1]				
Cheung *et al*[10], 2010	Canada	Retrospective	2000-2006	Control	50	67 ± 13	√	√	√	√
				CKD	50	71 ± 13				
				ESRD	50	68 ± 12				
Hung *et al*[25], 2014	Taiwan	Retrospective	2007	Control	6322	54.6 ± 13.3	√	-	-	-
				ESRD	110	NR				
Sood *et al*[9], 2012	United States	Retrospective	2007	Control	347245	NR	√	-	-	-
				CKD	35985	NR				
				ESRD	14983	NR				
Tsai *et al*[16], 1996	Taiwan	Prospective	1991-1994	Control	640	55.7 ± 16.2[2]	√	√	√	-
				ESRD	58	64.1 ± 11.4[2]				
Zuckerman *et al*[26], 1985	United States	Retrospective	1980-1983	Control	423	63 (16-96)[3]	-	-	√	-
				CKD (mix)	59	57 (24-84)[3]				

[1]Data expressed as mean ± SEM (standard error of mean); [2]Data expressed as mean ± SD (standard deviation); [3]Data expressed as median (interquartile range). NR: Not reported; CKD: Chronic kidney disease; ESRD: End-stage renal disease.

Table 3 Stars based on the Modified Newcastle-Ottawa Scale

Ref.	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Total (*)
Boyle *et al*[17], 1983	*	*	-	*	*		4
Cheung *et al*[10], 2010	*	*	*	*	*	*	6
Hung *et al*[25], 2014	*	*	-	-	-		2
Sood *et al*[9], 2012	*	*	-	-	-		2
Tsai *et al*[16], 1996	*	*	*	-	*	-	4
Zuckerman *et al*[26], 1985	*	*	-	-	-	*	3

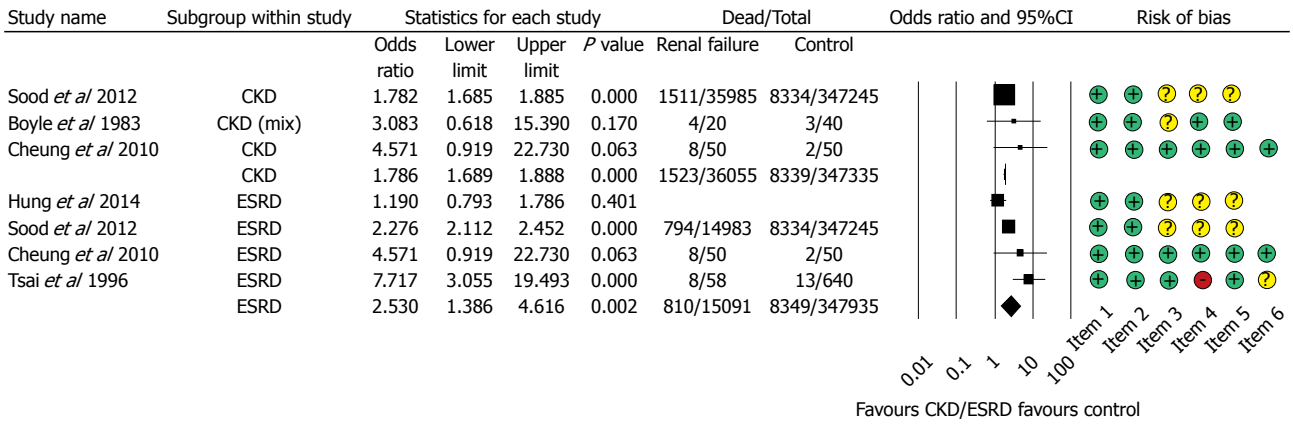

Figure 2 Forest plot representing the differences in mortality in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

most recent articles the OR is decreasing with the time (regression coefficient: *b* = -0.0548; 95%CI: -0.0968 to -0.0128; *P* = 0.0105; r-analog: 0.2, Supplementary Figure 2A). The number of required units for transfusion has not changed since the 1980s (*b* = -0.0028; 95%CI: -0.0242 to -0.0186; *P* = 0.7972; r-analog: 0.00, Supplementary Figure 2B). Based on data from 4 articles, no difference in rebleeding rate could be observed in the last 30 years (*b* = 0.0027; 95%CI: -0.0353 to 0.03; *P* = 0.8726; r-analog: 0.00, Supplementary Figure 2C).

On the score based on the Newcastle-Ottawa Scale, articles were assigned between 2 and 6 stars out of a maximum of 6 stars (Table 3). There was a low risk of bias in representativeness in the study and the control population; it received 100% (Figure 7). With regard to ascertaining exposure, 33% of the articles represented a low risk of bias, while 66% had an unclear risk of bias. In these articles CKD and ESRD were not clearly defined, or patients were sorted based on a code system. With regard to a comparison of age, half of the articles contained no clear data on

Study name	Subgroup within study	Statistics for each study				Difference in means and 95%CI	Risk of bias
		Difference in means	Lower limit	Upper limit	*P* value		
Cheung *et al* 2010	CKD	-1.200	-2.515	0.115	0.074		
Tsai *et al* 1996	ESRD	-1.670	-3.708	0.368	0.108		
Cheung *et al* 2010	ESRD	-2.700	-4.614	-0.786	0.006		
Boly *et al* 1983	CKD (mix)	-5.300	-10.436	-0.164	0.043		
		-1.863	-2.915	-0.812	0.001		

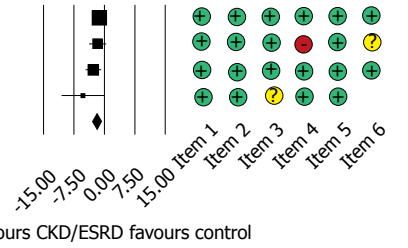

Figure 3 Forest plot representing the required units of transfusion in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for the difference in standardized mean values reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

Study name	Subgroup within study	Outcome	Statistics for each study				Exposed/Total		Odds ratio and 95%CI	Risk of bias
			Odds ratio	Lower limit	Upper limit	*P* value	Cases	Controls		
Cheung *et al* 2010	CKD	Rebleeding	1.194	0.371	3.841	0.766	7/50	6/50		
Tsai *et al* 1996	ESRD	Rebleeding	1.691	0.487	5.869	0.408	3/58	20/640		
Zuckerman *et al* 1985	CKD (mix)	Rebleeding	2.864	1.476	5.555	0.002	15/59	45/423		
Cheung *et al* 2010	ESRD	Rebleeding	4.495	1.610	12.545	0.004	19/50	6/50		
			2.510	1.521	4.144	0.000	44/217	77/1163		

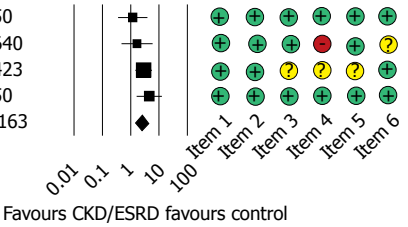

Figure 4 Forest plot representing the rebleeding rate in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

Study name	Subgroup within study	Statistics for each study				Difference in means and 95%CI	Risk of bias
		Difference in means	Lower limit	Upper limit	*P* value		
Cheung *et al* 2010	CKD	-8.400	-20.020	3.220	0.157		
Boyle *et al* 1983	CKD (mix)	-14.300	-23.636	-4.964	0.003		
Cheung *et al* 2010	ESRD	-17.400	-30.556	-4.244	0.010		
		-13.254	-19.623	-6.886	0.000		

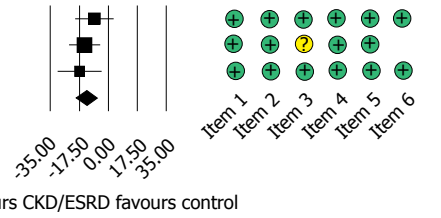

Figure 5 Forest plot representing the differences in length of hospitalization in gastrointestinal bleeding patients with normal and impaired renal function. Size of squares for the difference in standardized mean values reflects weight of trial in pooled analysis. Horizontal bars represent 95%CI. CKD: Chronic kidney disease; ESRD: End-stage renal disease.

the groups and there was a significant difference in the ages of the ESRD and control groups in Tsai *et al*[16]. 50% of the articles reported data on taking ulcerogenic drugs; the other half represented an unclear risk of bias. The follow-up time for rebleeding was analysed in 3 articles; only one did not report this clearly.

DISCUSSION

CKD is a term that covers all degrees of decreased renal function (mild, moderate, and severe chronic kidney disease), where the GFR is lower than 60 mL/min for longer than 3 mo[23]. CKD is a worldwide public health problem, with both incidence and prevalence rising and the main causes being diabetes mellitus and high blood pressure. ESRD patients requiring haemodialysis or peritoneal dialysis 3 times a week represent a high burden and cost for the health care system. As the prevalence of hypertension and diabetes mellitus, the most important etiological factors for CKD and ESRD is increasing worldwide, we predict that GI bleeding with CKD will be a growing problem. According to Ohmori *et al*[13] the number of patients on hemodyalisis has tripled between 1990 and 2010. This is the first meta-analysis to report on the severity of complications after GI bleeding in patients with CKD or ESRD and normal renal function groups. Based on a systematic search in 3 databases, we were able to include 6 articles, which contained data on 406035 patients, of whom 51315 had impaired renal function. A higher prevalence of peptic ulcers was reported among ESRD patients undergoing long-term dialysis[27,28]. The elevated risk

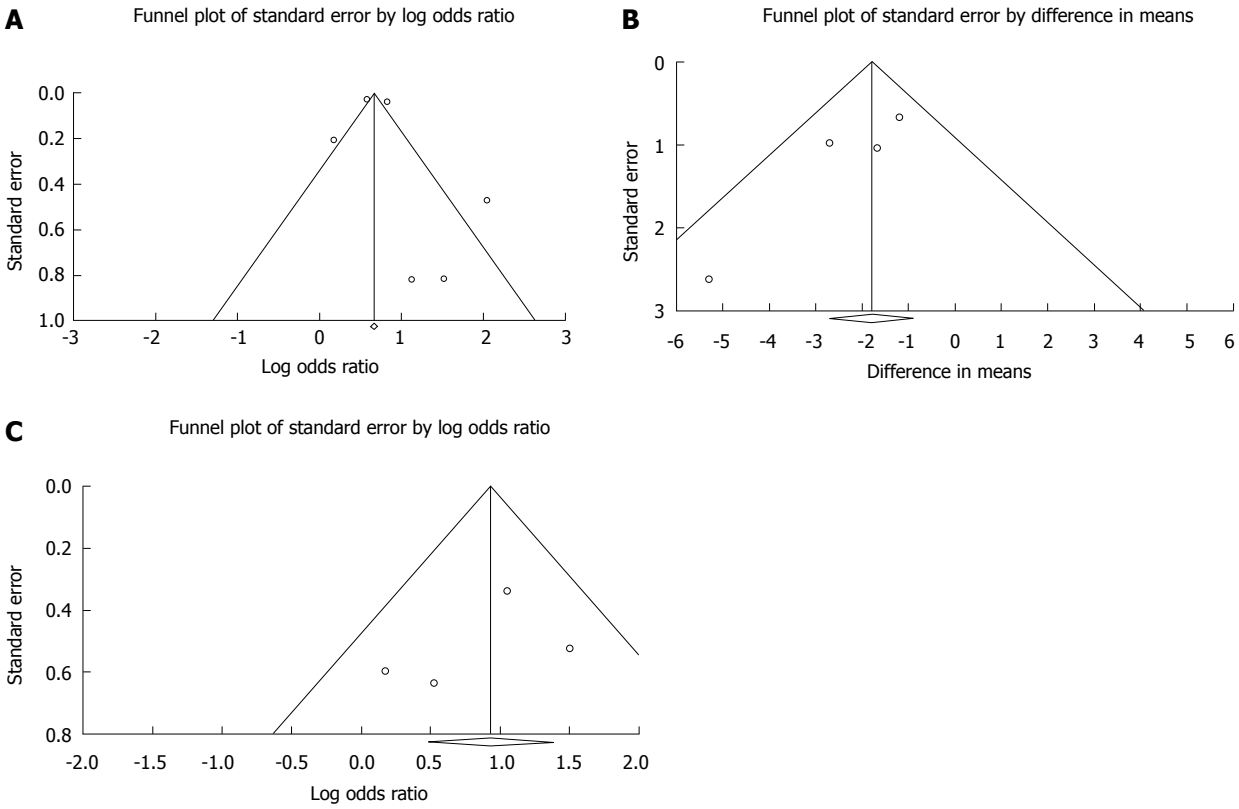

Figure 6 Funnel plot. A: Funnel plot of mortality; B: Funnel plot of required transfusion; and C: Funnel plot of rebleeding.

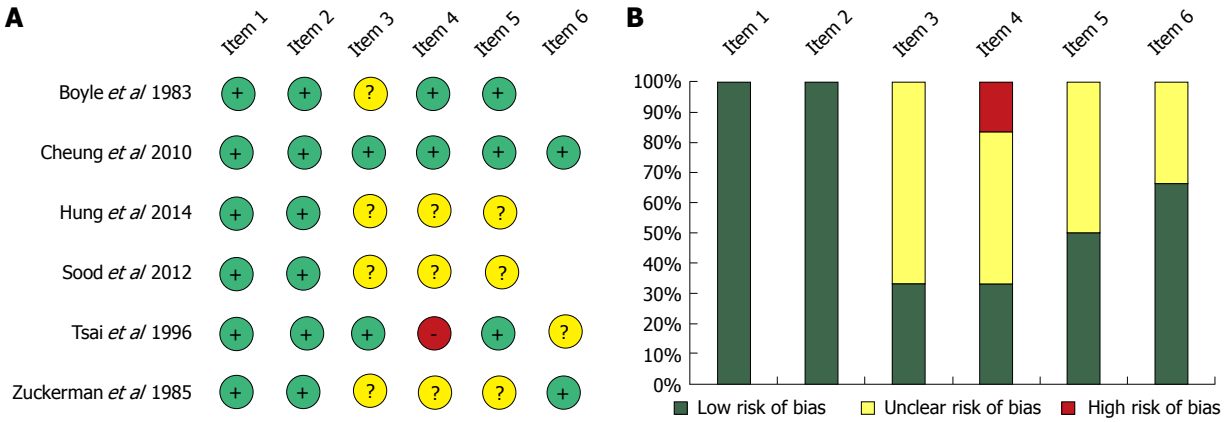

Figure 7 Risk assessment of articles included in the meta-analysis based on the modified Newcastle-Ottawa Scale (A); Risk of bias assessment graph (B).

for GI bleeding in CKD and ESRD patients is also well known[29]. The most frequent causes of lower GI bleeding in this population have been described; diverticulosis, haemorrhoids, and ischaemic colitis have been identified in addition to angioectasias[30], but no cohort study has been conducted on this topic yet. Although we did not intend to narrow our search to upper GI bleeding, the articles eligible for our inclusion criteria contained data only on patients with upper GI bleeding, and no studies with lower GI bleeding met our inclusion criteria. Only a few of the studies detailed the endoscopic findings and cause of bleeding. Cheung *et al*[10] included only peptic ulcer bleeding patients, while the study of Hung *et al*[25] examined only esophageal variceal bleeding. Tsai *et al*[16] found that erosive gastritis was significantly higher in ESRD group, while Boyle *et al*[17] saw gastric ulcer as the most common cause of bleeding in the impaired renal function group, but it was not significant compared to controls. Zuckerman *et al*[26] found significantly more angiodysplasia and erosive esophagitis in the impaired renal function group.

Based on the pooled data, we found that ESRD increases mortality 2.5 times while CKD increases it 1.8 times in GI bleeding compared to the controls with normal renal function, but these ORs are not

significantly different. Weng *et al*[31] reported that ESRD patients admitted with primary upper GI bleeding have a profoundly increased risk of in-hospital mortality. Using a large multi-centre database, Sood *et al*[9] reported that the in-hospital mortality risk is 50% higher in CKD patients and 3 times greater in ESRD patients. Holden *et al*[32] reported that the incidence rate of major bleeding episodes in haemodialyzed patients was 2.5% per person-year and that use of aspirin and/or warfarin increased this risk. Based on the result of the meta-regression the mortality-rate of GI bleeding has improved since the 1980s. It is likely one of the reasons for the heterogeneity of the data. Inhomogen patient groups also result in a significant bias. However the sensitivity analysis showed that none of the articles influences significantly the pooled OR.

Cardiovascular disease, current smoking[33] and even haemostasis disorders[34] may play a role in the background of higher risk for GI bleeding in ESRD patients. Unfortunately only few of the analysed articles detailed the other comorbidities of the GI bleeding patients. In the article of Cheung *et al*[10]. there was no significant difference in the comorbidities between ESRD, CKD and normal renal function group. More people in CKD and ESRD groups suffered from hypertension, diabetes mellitus and platelet abnormalities in the study of Sood *et al*[9], while the cirrhosis was less common than in controls. Volume replacement and blood transfusion are important parts of the therapy of GI bleeding. This meta-analysis demonstrated that patients with chronic impaired renal function develop 2.5 times more rebleeding episodes and require almost 2 more red blood cell units for transfusion than the control group. Patients with impaired renal function spent more time in hospital than the control group.

There are several limitations to this study; therefore, the results of this meta-analysis should be regarded with caution. Unfortunately, only a low number of articles was found on this topic, with half of them written in the 1980s and 1990s. In the recent articles, CKD and ESRD groups were separated, but in the earlier publications these groups were mixed, leading to a bias in our analysis, and the definition of GFR was also not mentioned. The diagnosis was based on elevated creatinine level. Hung *et al*[25] only involved patients with cirrhosis and the mortality rate was monitored up to 6 wk, while hospital mortalities were presumably included in the other articles. Publications with rebleeding data did not follow patients for the same time interval, and 1 paper did not report on the follow-up time. The strength of this meta-analysis is the high number of patients.

Our results have demonstrated that patients with ESRD show higher mortality during GI bleeding. CKD patients require more transfusion, and the rebleeding rate is also more elevated than that in patients with normal renal function. Because of these severe conditions, the LOH is also longer. Patients with ESRD or CKD should be observed more carefully due to the elevated complication rate. In this meta-analysis we wanted to highlight the importance of this clinical problem and we believe that it needs further scientific research. In order to understand the effect of CKD/ESRD and other comorbidities on the outcomes of GI bleeding in more details, observational trials, and registries on GI bleeding should be developed.

ARTICLE HIGHLIGHTS

Research background

Chronic kidney disease is a significant comorbidity, which can worsen the outcomes of gastrointestinal (GI) bleeding.

Research motivation

We wanted to understand the role of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the natural history of GI bleeding.

Research objectives

Our goal was to investigate the influence of CKD and ESRD on the outcomes of GI bleeding, based on all available data published in this topic.

Research methods

A comprehensive search was carried out in PubMed, Embase and Cochrane Library databases for studies detailing the outcomes of GI bleeding in the context of kidney functions. We used the PRISMA P protocol, registered our project through PROSPERO and assessed the quality of the included articles by using the Newcastle-Ottawa Scale, to ensure that this meta-analysis is done to the highest possible standards. The statistical calculations were performed with Comprehensive Meta-Analysis software, using the random effects model (DerSimonian-Laird method).

Research results

In this analysis 51315 patients with CKD and 354720 controls were included (6 articles). We found that the mortality of GI bleeding was significantly worse in CKD and ESRD with an OR of 1.79 and 2.53 respectively. Patients with kidney disease needed significantly more transfusion with a MD of 1.86 and the rebleeding rate was significantly worse in the group with impaired kidney function with an OR of 2.51. Patients with impaired kidney function needed significantly longer hospitalization with a MD of 13.25.

Research conclusions

This is the first meta-analysis and systematic review in this topic, which quantifies kidney disease as a negative risk factor in GI bleeding. GI bleeding in patients with chronic renal failure significantly increases the mortality rate, rebleeding rate, length of hospitalization, and require more blood transfusion compared to patients with normal kidney functions. Kidney disease significantly worsens the outlook of patients presenting with GI bleeding. Patients with chronic kidney disease will need to be treated with more caution due to the worse outcomes of GI bleeding. Close monitoring of the fluid balance and kidney functions, careful fluid therapy and prevention of acute kidney injury in these patients may improve the outcomes of GI bleeding.

Research perspectives

Although CKD, ESRD, and other comorbidities are major risk factors for unfavorable outcomes in GI bleeding, their roles are not well investigated nor understood and they need further scrutiny. We would better understand the role of CKD in ESRD in GI bleeding from analysis of extensive data from large multicenter and multinational observational studies and registries accurately recording the outcomes and the kidney functions.

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The present paper is dedicated to the 650th anniversary of the founding of the University of Pécs, Hungary.

REFERENCES

1 **Cutler JA**, Mendeloff AI. Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. *Dig Dis Sci* 1981; **26**: 90S-96S [PMID: 6985341]
2 **Vreeburg EM**, Snel P, de Bruijne JW, Bartelsman JF, Rauws EA, Tytgat GN. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. *Am J Gastroenterol* 1997; **92**: 236-243 [PMID: 9040198]
3 **Hussain H**, Lapin S, Cappell MS. Clinical scoring systems for determining the prognosis of gastrointestinal bleeding. *Gastroenterol Clin North Am* 2000; **29**: 445-464 [PMID: 10836189 DOI: 10.1016/S0889-8553(05)70122-9]
4 **Zuccaro G Jr**. Management of the adult patient with acute lower gastrointestinal bleeding. American College of Gastroenterology. Practice Parameters Committee. *Am J Gastroenterol* 1998; **93**: 1202-1208 [PMID: 9707037 DOI: 10.1111/j.1572-0241.1998.00395.x]
5 **Rockall TA**, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38**: 316-321 [PMID: 8675081]
6 **Lin CC**, Wang HP, Wu MS, Ho WC, Lee H, Lin JT. The etiology and clinical characteristics of acute lower gastrointestinal bleeding in patients hospitalized for comorbid illnesses. *Hepatogastroenterology* 2006; **53**: 395-398 [PMID: 16795980]
7 **Laeeq SM**, Tasneem AA, Hanif FM, Luck NH, Mandhwani R, Wadhva R. Upper Gastrointestinal Bleeding in Patients with End Stage Renal Disease: Causes, Characteristics and Factors Associated with Need for Endoscopic Therapeutic Intervention. *J Transl Int Med* 2017; **5**: 106-111 [PMID: 28721343 DOI: 10.1515/jtim-2017-0019]
8 **Kuo CC**, Kuo HW, Lee IM, Lee CT, Yang CY. The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a population-based cohort study. *BMC Nephrol* 2013; **14**: 15 [PMID: 23324652 DOI: 10.1186/1471-2369-14-15]
9 **Sood P**, Kumar G, Nanchal R, Sakhuja A, Ahmad S, Ali M, Kumar N, Ross EA. Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding. *Am J Nephrol* 2012; **35**: 216-224 [PMID: 22310659 DOI: 10.1159/000336107]
10 **Cheung J**, Yu A, LaBossiere J, Zhu Q, Fedorak RN. Peptic ulcer bleeding outcomes adversely affected by end-stage renal disease. *Gastrointest Endosc* 2010; **71**: 44-49 [PMID: 19595311 DOI: 10.1016/j.gie.2009.04.014]
11 **Gheissari A**, Rajyaguru V, Kumashiro R, Matsumoto T. Gastrointestinal hemorrhage in end stage renal disease patients. *Int Surg* 1990; **75**: 93-95 [PMID: 2379997]
12 **Docherty E**, Koulaouzidis A, Douglas S, Plevris JN. Use of small bowel capsule endoscopy in patients with chronic kidney disease: experience from a University Referral Center. *Ann Gastroenterol* 2015; **28**: 99-104 [PMID: 25608445]
13 **Ohmori T**, Konishi H, Nakamura S, Shiratori K. Abnormalities of the small intestine detected by capsule endoscopy in hemodialysis patients. *Intern Med* 2012; **51**: 1455-1460 [PMID: 22728474]
14 **Karagiannis S**, Goulas S, Kosmadakis G, Galanis P, Arvanitis D, Boletis J, Georgiou E, Mavrogiannis C. Wireless capsule endoscopy in the investigation of patients with chronic renal failure and obscure gastrointestinal bleeding (preliminary data). *World J Gastroenterol* 2006; **12**: 5182-5185 [PMID: 16937529 DOI: 10.3748/wjg.v12.i32.5182]
15 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]
16 **Tsai CJ**, Hwang JC. Investigation of upper gastrointestinal hemorrhage in chronic renal failure. *J Clin Gastroenterol* 1996; **22**: 2-5 [PMID: 8776085]
17 **Boyle JM**, Johnston B. Acute upper gastrointestinal hemorrhage in patients with chronic renal disease. *Am J Med* 1983; **75**: 409-412 [PMID: 6604455]
18 **Hozo SP**, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13 [PMID: 15840177 DOI: 10.1186/1471-2288-5-13]
19 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833]
20 **Higgins JP,** Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011
21 **Viel JF**, Pobel D, Carré A. Incidence of leukaemia in young people around the La Hague nuclear waste reprocessing plant: a sensitivity analysis. *Stat Med* 1995; **14**: 2459-2472 [PMID: 8711281]
22 **Wells G**, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2010
23 **Stevens PE**, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158**: 825-830 [PMID: 23732715 DOI: 10.7326/0003-4819-158-11-201306040-00007]
24 **Alvarez L**, Puleo J, Balint JA. Investigation of gastrointestinal bleeding in patients with end stage renal disease. *Am J Gastroenterol* 1993; **88**: 30-33 [PMID: 8420270]
25 **Hung TH**, Tseng CW, Tseng KC, Hsieh YH, Tsai CC, Tsai CC. Is end stage renal disease a risk factor for the mortality of cirrhotic patients with esophageal variceal bleeding? *Hepatogastroenterology* 2014; **61**: 1871-1875 [PMID: 25713881]
26 **Zuckerman GR**, Cornette GL, Clouse RE, Harter HR. Upper gastrointestinal bleeding in patients with chronic renal failure. *Ann Intern Med* 1985; **102**: 588-592 [PMID: 3872616]
27 **Sugimoto M**, Sakai K, Kita M, Imanishi J, Yamaoka Y. Prevalence of Helicobacter pylori infection in long-term hemodialysis patients. *Kidney Int* 2009; **75**: 96-103 [PMID: 18843261 DOI: 10.1038/ki.2008.508]
28 **Khedmat H**, Ahmadzad-Asl M, Amini M, Lessan-Pezeshki M, Einollahi B, Pourfarziani V, Naseri MH, Davoudi F. Gastroduodenal lesions and Helicobacter pylori infection in uremic patients and renal transplant recipients. *Transplant Proc* 2007; **39**: 1003-1007 [PMID: 17524875 DOI: 10.1016/j.transproceed.2007.03.034]
29 **Luo JC**, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC, Lee FY, Lee SD. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. *CMAJ* 2011; **183**: E1345-E1351 [PMID: 22083684 DOI: 10.1503/cmaj.110299]
30 **Kalman RS**, Pedrosa MC. Evidence-based review of gastrointestinal bleeding in the chronic kidney disease patient. *Semin Dial* 2015; **28**: 68-74 [PMID: 25215610 DOI: 10.1111/sdi.12301]
31 **Weng SC**, Shu KH, Tarng DC, Tang YJ, Cheng CH, Chen CH, Yu TM, Chuang YW, Huang ST, Sheu WH, Wu MJ. In-hospital mortality risk estimation in patients with acute nonvariceal upper gastrointestinal bleeding undergoing hemodialysis: a retrospective cohort study. *Ren Fail* 2013; **35**: 243-248 [PMID: 23336331 DOI: 10.3109/0886022X.2012.747140]
32 **Holden RM**, Harman GJ, Wang M, Holland D, Day AG. Major bleeding in hemodialysis patients. *Clin J Am Soc Nephrol* 2008; **3**: 105-110 [PMID: 18003768 DOI: 10.2215/cjn.01810407]
33 **Wasse H**, Gillen DL, Ball AM, Kestenbaum BR, Seliger SL, Sherrard D, Stehman-Breen CO. Risk factors for upper

gastrointestinal bleeding among end-stage renal disease patients. *Kidney Int* 2003; **64**: 1455-1461 [PMID: 12969166 DOI: 10.1046/j.1523-1755.2003.00225.x]

34 **Jalal DI**, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost* 2010; **36**: 34-40 [PMID: 20391294 DOI: 10.1055/s-0030-1248722]

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

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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, $p = 0.119$).

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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

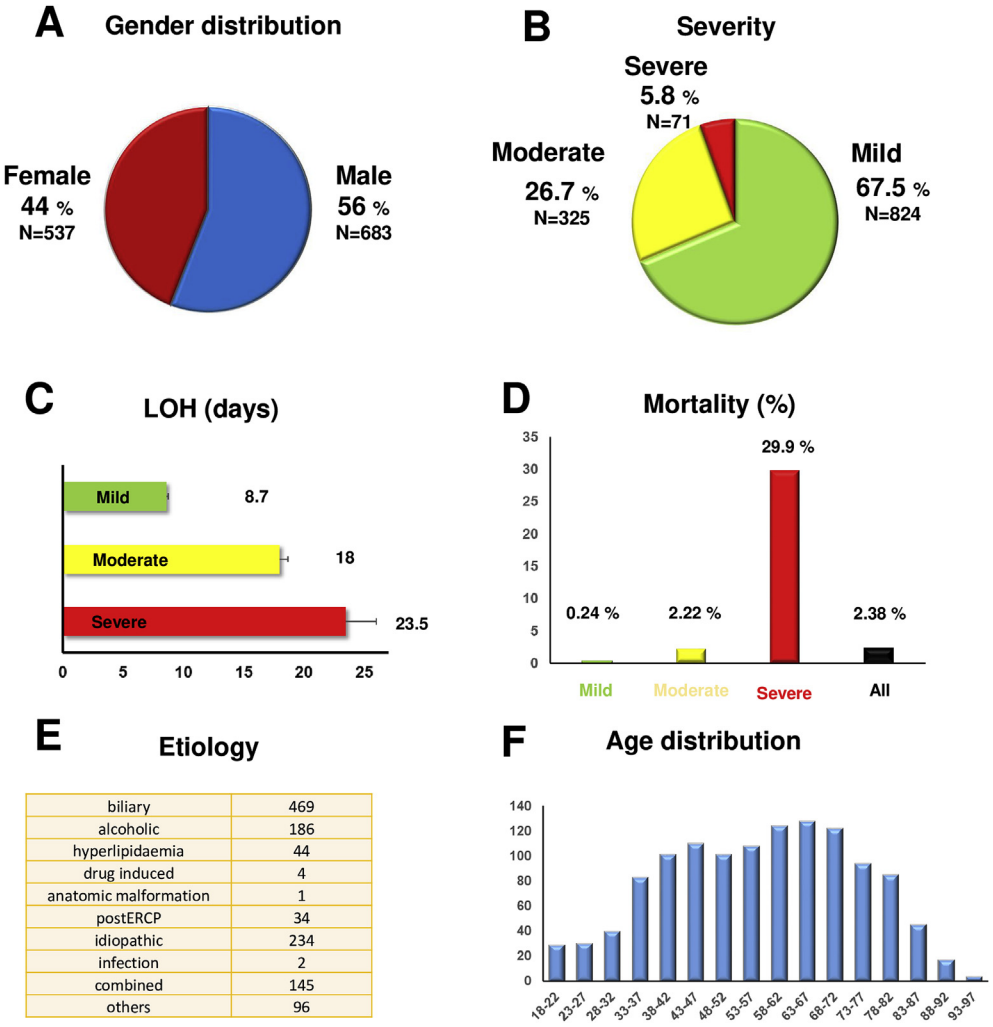
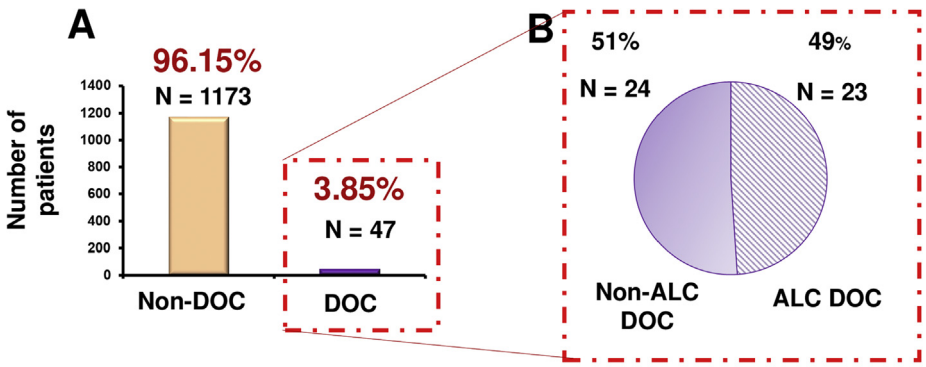


Fig. 1. A. Overall gender distribution. 1.B. Distribution based on severity. 1.C. The average length of hospitalization in days. 1.D. Overall mortality and mortality based on severity classes. 1.E. Distribution based on the etiology of acute pancreatitis. 1.F. Age distribution of the population.



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Type of DOC

confusion	16
delirium	19
alcohol withdrawal	9
convulsion	3

Alcohol-related: 23

confusion	1
delirium	12
alcohol withdrawal	9
convulsion	1

Etiology

alcohol	23
sepsis	6
dementia	9
ischemia	3
idiopathic	4
hypoglycaemia	1
Impairment of salt and water balance	1

Non-alcohol related: 24

confusion	15
delirium	7
alcohol withdrawal	0
convulsion	2

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

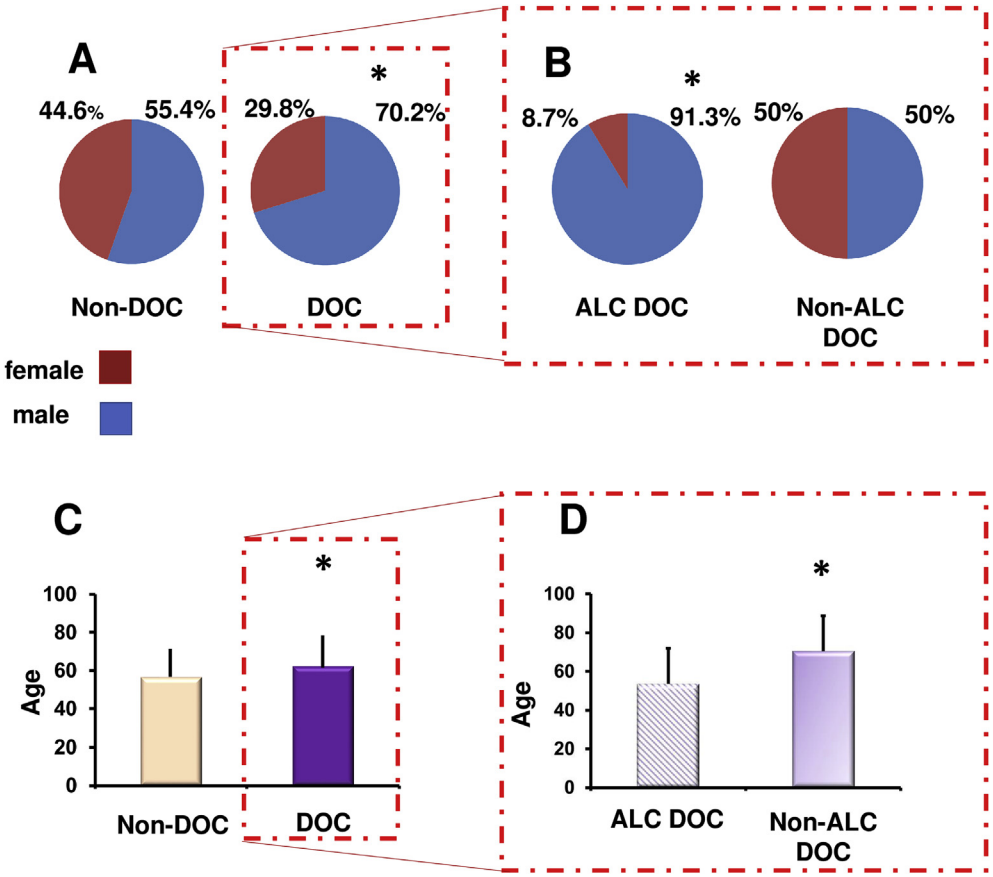

Fig. 3. A Sex distribution of disturbance of consciousness (DOC) and Non-DOC groups (Compared with Chi-squared test). Fig. 3B Sex distribution of alcohol-related DOC (ALC DOC) and non-alcohol related (Non-ALC DOC) groups (Compared with Fisher-test). 3.C Age distribution of DOC and Non-DOC groups (Compared 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

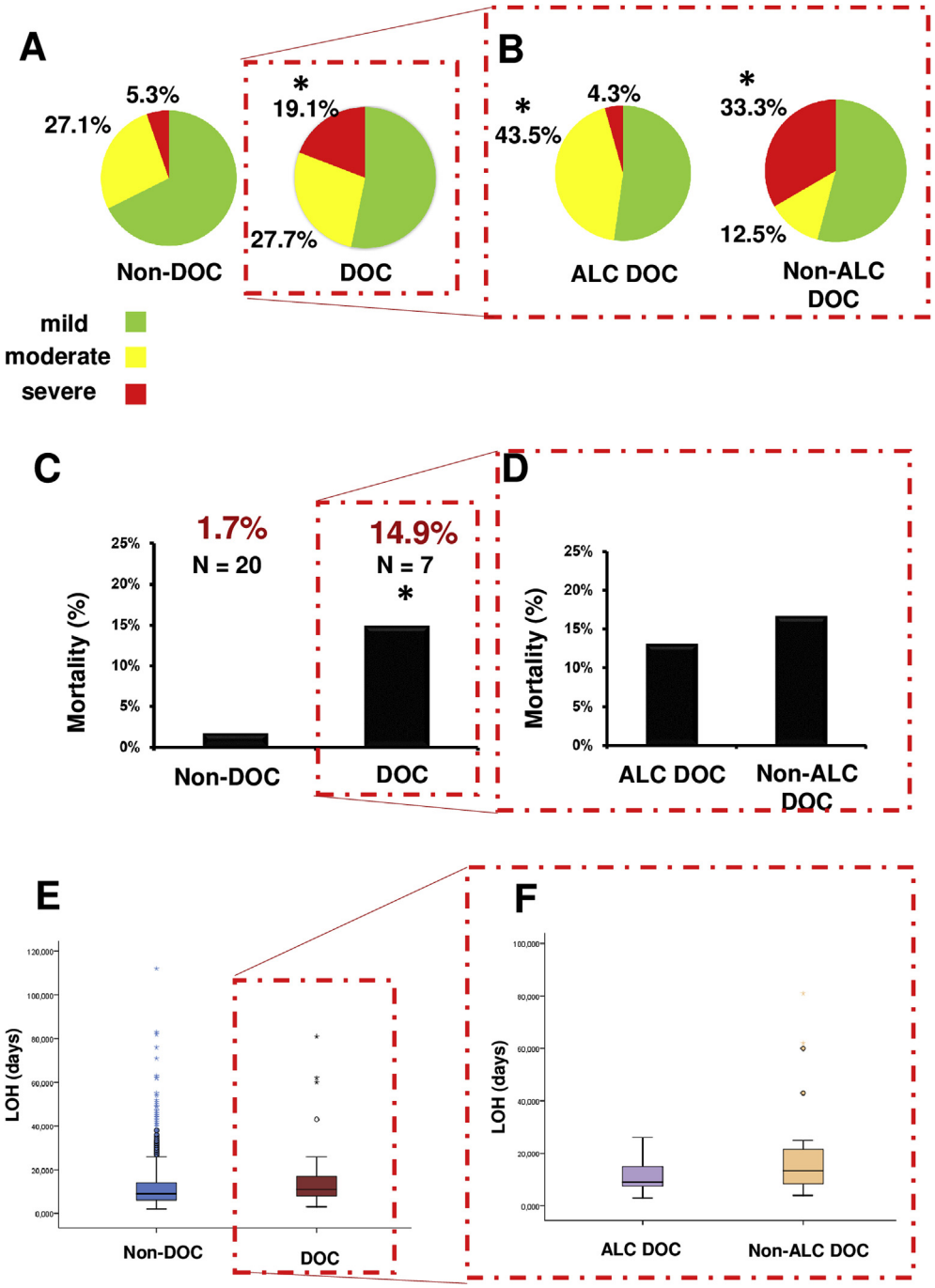

Fig. 4. A Distribution of severity of pancreatitis in disturbance of consciousness (DOC) and Non-DOC groups (Compared with Fisher test). 4.B Distribution of severity of acute pancreatitis of alcohol-related DOC (ALC DOC) and non-alcohol related (Non-ALC DOC) groups (Compared with Fisher test). 4.C Distribution 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.

Author contributions

Hegyi P., Párniczky A., Czakó L., Vincze Á., Szentesi A. and Mikó A. designed the research and the study concept; Izbéki F., Gajdán L., Gódi Sz., Illés A., Sarlós P. Illés D., Varjú P., Márta K., Török I., Papp M., Erőss B., Vincze Á., Vitális Zs., Bod B., Hamvas J., Lillik V., Márton Zs., Szepes Z. and Takács T., performed the acquisition of data; Farkas N. analyzed and interpreted the data; Hágendorn R, Farkas N, Hegyi P, and Mikó A wrote the paper; Izbéki F., Gajdán L., Gódi Sz., Illés A., Sarlós P supervised the study; all of the co-authors conducted a critical revision of the manuscript for important intellectual content; all of the co-authors granted final approval of the version of the article to be published.

Declaration of competing interest

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

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Appendix A. Supplementary data

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

References

[1] Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015;386:85–96.
[2] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
[3] Parniczky A, Kui B, Szentesi A, Balazs A, Szucs A, Mosztbacher D, et al. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. PloS One 2016;11:e0165309.
[4] Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–52.
[5] Dobszai D, Matrai P, Gyongyi Z, Csupor D, Bajor J, Eross B, et al. Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis. World J Gastroenterol 2019;25:729–43.
[6] Marta K, Lazarescu AM, Farkas N, Matrai P, Cazacu I, Ottoffy M, et al. Aging and comorbidities in acute pancreatitis: a meta-analysis and systematic review based on 194,702 patients. Front Physiol 2019;10:328.
[7] Miko A, Farkas N, Garami A, Szabo I, Vincze A, Veres G, et al. Preexisting diabetes elevates risk of local and systemic complications in acute pancreatitis: systematic review and meta-analysis. Pancreas 2018;47:917–23.
[8] Szakacs Z, Gede N, Pecsi D, Izbeki F, Papp M, Kovacs G, et al. Aging and comorbidities in acute pancreatitis: a cohort-analysis of 1203 prospectively collected cases. Front Physiol 2018;9:1776.
[9] Szentesi A, Parniczky A, Vincze A, Bajor J, Godi S, Sarlos P, et al. Multiple hits in acute pancreatitis: components of metabolic syndrome synergize each other's deteriorating effects. Front Physiol 2019;10:1202.
[10] McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. J Neurol Neurosurg Psychiatr 2008;79:854–62.
[11] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–22.
[12] Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168:27–32.
[13] Sun GH, Yang YS, Liu QS, Cheng LF, Huang XS. Pancreatic encephalopathy and Wernicke encephalopathy in association with acute pancreatitis: a clinical study. World J Gastroenterol 2006;12:4224–7.
[14] Faught DD. Delirium: the nurse's role in prevention, diagnosis, and treatment. Medsurg Nurs: Off J Acad Med Surg Nurs 2014;23:301–5.
[15] Volland J, Fisher A, Drexler D. Preventing and identifying hospital-acquired delirium. Nursing 2020;50:32–7.
[16] Lahariya S, Grover S, Bagga S, Sharma A. Delirium in patients admitted to a cardiac intensive care unit with cardiac emergencies in a developing country: incidence, prevalence, risk factor and outcome. Gen Hosp Psychiatr 2014;36:156–64.
[17] Trogrlic Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PH, et al. A systematic review of implementation strategies for assessment, prevention, and management of icu delirium and their effect on clinical outcomes. Crit Care 2015;19:157.
[18] Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, et al. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2014;28:1459–66.
[19] D'Onofrio G, Rathlev NK, Ulrich AS, Fish SS, Freedland ES. Lorazepam for the prevention of recurrent seizures related to alcohol. N Engl J Med 1999;340:915–9.
[20] Gershkovich P, Wasan KM, Ribeyre C, Ibrahim F, McNeill JH. Effect of variations in treatment regimen and liver cirrhosis on exposure to benzodiazepines during treatment of alcohol withdrawal syndrome. Drugs Context (US) 2015;4:212287.
[21] Garpestad E, Devlin JW. Polypharmacy and delirium in critically ill older adults: recognition and prevention. Clin Geriatr Med 2017;33:189–203.
[22] Godfrey M, Green J, Smith J, Cheater F, Inouye SK, Hurst K, et al. Process of implementing and delivering the prevention of delirium system of care: a mixed method preliminary study. BMC Geriatr 2019;20:1.