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

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I.   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. 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.

Acute pancreatitis (AP) is a leading cause of hospital admissions worldwide. The disease can be traced back to various causes, which can vary in severity. According to the severity of the disease, we distinguish between mild, moderate and severe cases. Mortality in severe cases is much higher, approximately 30%. As the mortality of severe cases is high, the disease has been in the focus of research in recent decades. 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. 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 Hypotheses/Aims

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

II.2 Methods

This study was conducted using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). 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.

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 end-stage renal disease (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. 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. All meta-analytic calculations were performed with Comprehensive Meta-Analysis software (Version 3.0, Biostat Inc.) using the random-effects model (DerSimonian-Laird method). 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 $I2$ statistics. Based on the Cochrane Handbook, $I2 = 100\% \times (Q - df)/Q$, with $I2$ representing the magnitude of the heterogeneity (moderate: 30%-60%; substantial: 50%-90%; considerable: 75%-100%). 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. 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. 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. The Newcastle-Ottawa Scale (NOS) adjusted to our study design was used to assess the quality of nonrandomized cohort studies. The selection, comparability and outcome data were assessed based on 6 items 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 were applied, we assigned no points. We used the classical definition of CKD, 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.3 Results

1063 articles (EMBASE: 589; PubMed: 459; Cochrane: 15) were found altogether through database searches. 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. The remaining 5 and one other eligible record which was found in reference lists were 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. Data on mortality was available in all of the articles included. 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, $P = 0.002$). 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, $P < 0.001$). It was possible to retrieve data on the rebleeding rate from 3 articles. 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, $P < 0.001$). 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, $P < 0.001$). 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; $I2 = 0\%$; $P = 0.577$). 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. 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). 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). 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.

II.4 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. 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 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. 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. The elevated risk for GI bleeding in CKD and ESRD patients is also well known. 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, 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. 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. 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. 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. 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 Aims/Hypothesis

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.2 Methods

The Hungarian Pancreatic Study Group (HPSG) established a prospective international registry containing AP patients' data. For this HPSG cohort study data of 1220 patients were used, since they contained data about the level of consciousness during hospitalization. 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). 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. 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.3. Results

A total of 1220 cases from 20 centers were analyzed. 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%. 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). 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%. From the 1220 patients of the HPSG registry, 47 patients (3.9%) developed DOC. 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. 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). 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). From the registered 47 patients with DOC, 23 (48.9%) cases were ALC DOC, whereas 24 (51.1%) cases were Non-ALC DOC. 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). 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. Patients with Non-ALC DOC were older than patients with ALC DOC (70.5 ± 18.4 vs. 53.5 ± 15 years, p: 0.002). 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), 8.8 times higher mortality (14.9% vs.1.7%, n: 7/ 47 vs. n: 20/1173, p <

0.001), and a longer LOH in the DOC group (Me: 11; IQR: 8-17 days vs. Me: 9; IQR: 6-13 days, p: 0.049) 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), $p < 0.001$. Mortality showed no difference between the analyzed groups (n: 3 vs. n: 4). 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).

III.4 Discussion

Hospital-acquired delirium often remains unnoticed, because its symptoms resemble dementia and depression, further complicating the diagnosis. 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. 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.

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. 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 PhD 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.

Disorder of consciousness may develop 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.

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