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Sex and acute oesophageal variceal bleeding-related in-hospital mortality: a 15-year retrospective study

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Abstract. – OBJECTIVE: The relationship between in-hospital mortality (IHM) and acute oesophageal variceal bleeding (AOEVB) has not been fully assessed. The aim of this study was to establish the association between sex and mortality for patients hospitalized with AOEVB.

PATIENTS AND METHODS: We analyzed hospitalizations from the Italian Health Ministry database by identifying all patients discharged with AOEVB from January 2001 to December 2015. A total of 144,943 hospitalizations were for oesophageal varices, but only 24,570 emergency admissions with AOEVB coded as the primary or secondary diagnosis were included for analysis. Factors independently associated with IHM were evaluated by multilevel logistic regression.

RESULTS: Approximately half of the population was aged ≥ 65 years, and nearly 10% was diagnosed with hepatocellular carcinoma. Overall, the IHM was 11.8%, with 12.1% in males and 11.3% in females, increasing from 9.2% among subjects aged < 55 years to 18.9% among those aged ≥ 85 years. The crude risk of death was slightly higher among females; however, when age and clinical presentation were considered, female sex was associated with reduced mortality. For liver disease, the risk of death in women was lower only in those with non-alcoholic liver disease (odds ratio= 0.77, 0.66-0.89), but it was similar to that in men for unspecified, cancer and alcoholic liver disease. The risk declined over time and was increased in patients with multiple comorbidities.

CONCLUSIONS: AOEVB-related IHM decreased from 2001-2005 to 2011-2015. Factors affecting mortality included liver disease, age, sex, development of hepatocellular carcinoma and comorbidities.

Key Words:
Acute oesophageal variceal bleeding, In-hospital mortality, Sex, Comorbidity, ICD-9-CM coding.

Introduction

Analysis by sex is crucial to understand whether health outcomes are related to biological differences or whether they depend upon social, economic and cultural factors. Analysis by sex should include both chronic and acute conditions. Massive bleeding is a major, life-threatening clinical event, and death is potentially preventable, depending on different risk factors[1].

Acute oesophageal variceal bleeding (AOEVB), a frequent and often lethal complication of cirrhosis, occurs in up to 25% of patients and has a 6-week mortality rate of 15-20% for each episode[2,3]. Accordingly, early stabilization, triage to the appropriate level of care, medical and supportive management, early endoscopy for diagnosis, risk stratification, and therapeutic intervention are key determinants in the management of these patients to reduce mortality rates[2,3].

Because cirrhosis has a higher prevalence in males than females, its mortality rate has been reported to be higher in males, and alcohol abuse leading to cirrhosis appears to be more common in males than females. A recent Italian study analysed sex differences in chronic liver diseases in cohorts in 2001 and 2014[4]. In this study, the authors evaluated more than 12,000 patients, showing that chronic liver diseases were more common in young male patients and that hepatitis B virus (HBV) aetiology was preponderant for the male sex. Conversely, in the female group, abstainers decreased, and alcohol-related liver disease increased in the 2014 cohort compared to the 2001 cohort[4].

The aim of this study was to investigate the relationship among sex, comorbidity and the in-ho-

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spital mortality (IHM) rate of patients with acute AOEVB.

Patients and Methods

Patient Selection and Eligibility

The analysis included all hospital admissions for AOEVB between January 1, 2001, and December 31, 2015, recorded in all Italian regions. Data were obtained from the Italian National Hospital database provided by the Ministry of Health (Banca Dati SDO, Ministero della Salute, Direzione Generale della Programmazione Sanitaria). The national database includes all hospital discharge records (HDRs) of patients admitted to public and private hospitals in Italy.

The HDR lists included sex, age, date of hospital admission and discharge, department of admission and discharge, vital status at discharge (in-hospital death vs. discharged alive), the main diagnosis and up to 5 comorbidities, and up to 6 procedures/interventions based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The Ministry of Health removed patient names and other potential identifiers from the database available for this study to adhere to national rules on patient privacy and anonymity. A consecutive number for each patient was the only identifier allowed to analyse the database for possible recurrence of hospital admissions for the same patient.

AOEVB patients were identified using the following ICD-9-CM codes as first or second discharge diagnoses: 456.0 oesophageal varices with bleeding and 456.20 oesophageal varices in diseases classified elsewhere, with bleeding.

Table I. Characteristics of patients hospitalized for acute oesophageal variceal bleeding in Italy from 2001 to 2015.

	24,570 patients
Age class (years)	
<55	6,986
55-64	5,384
65-74	6,598
75-84	4,602
≥ 85	1,000
Sex	
Male	16,724
Female	7,846
Underlying liver disease	
Unspecified/other	5,955
Liver cancer	2,349
Alcoholic liver disease	5,402
Non-alcoholic liver disease	10,864
Severity of liver disease	
Complications mentioned	20,785
Not mentioned	3,785
Charlson Comorbidity Index	
0-1	20,543
2	2,904
≥ 3	1,123

Statistical Analysis

The analysis was limited to hard clinical indicators: fatal (death during hospitalization) and nonfatal (patient discharged alive) outcome. The modified version of the Charlson Comorbidity Index (CCI) adapted to ICD-9-CM codes[5] was applied to derive the overall comorbidity score after excluding mild/severe liver disease (present in all study subjects based on the selection criteria). The most common underlying liver diseases were identified from discharge codes: liver cancer (ICD9-CM 155), alcoholic liver diseases (155.0-155.3), and other specified liver diseases (571.4-571.9). The presence of decompensated liver disease was tracked by discharge codes for hepatic encephalopathy (572.2), hepatorenal syndrome (572.4), ascites (789.5), and spontaneous bacterial peritonitis (567.2).

Descriptive data are presented as absolute numbers, and percentages. Multilevel models were used to assess the influence of study variables on IHM. The odds ratio (OR) with 95% confidence interval (CI) was estimated after adjustment for age, sex, calendar period, underlying liver disease, decompensated disease, and CCI. Moreover, a relationship between sex and AOEVB-related IHM was analysed by classifying patients on the basis of underlying liver disease identified by ICD-9-CM. Further analyses were carried out, focusing on hospitalizations with AOEVB as the primary diagnosis or the first admission among subjects with multiple events throughout the study period. All analyses were performed using the statistical package Stata 13.

Results

During the study period, 144,943 patients were discharged with a diagnosis of AOEVB. Of these, 76,947 (53.1%) were urgent admissions, and only patients with a primary or secondary diagnosis of AOEVB (n=24,570) were included in the study population, with the number of males being 16,724 and females being 7,846. The patients' characteristics are summarized in Table I: ap-

proximately half were aged ≥ 65 years, and nearly 10% were diagnosed with hepatocellular carcinoma. IHM occurred in 11.8% of patients (2,905 patients: 12.1% males and 11.3% females), with an increasing trend from 9.2% (among subjects aged < 55 years) to 18.9% (among elderly subjects ≥ 85 years) (Table II). The crude risk of death was slightly higher among females, but when age and clinical presentation were considered, female sex was associated with reduced mortality. The risk of death increased in patients with a diagnosis of hepatocellular carcinoma, alcohol-related liver disease, decompensated liver disease, and although without a linear relationship, multiple comorbidities. The mortality rate declined over time. The relationship between female sex and AOEVB-related IHM is reported in Table III. The risk of IHM was reduced in women with non-alcoholic liver disease. Conversely, it was increased in those with alcoholic liver disease, although the relationship did not reach statistical significance (OR 1.21; 95% CI 0.98-1.50, p= 0.074).

Discussion

To our knowledge, this is the first Italian study evaluating sex differences in AOEVB-related IHM involving a comprehensive analysis of a national database. We found that in female subjects, the risk of AOEVB-related IHM was lower for non-alcoholic liver disease, but it appeared to be increased for alcoholic liver disease. Similarly, a recent Korean study of 318,224 subjects aged 20 to 94 years evaluated whether non-alcoholic fatty liver disease (NAFLD) was associated with overall increased mortality and cause-specific death. In women, NAFLD was associated with death independent of cancer, cardiovascular and liver diseases[6].

AOEVB-related IHM is associated with morbidity and mortality rates higher than those due to other causes of gastrointestinal bleeding. Mortality occurs in approximately 30% of cases at the first bleeding episode and increases to 70% of cases among survivors with bleeding relapses. The survival rate at the one-year follow-up after vari-

Table II. Factors associated with in-hospital mortality among admissions with acute oesophageal variceal bleeding in Italy from 2001 to 2015. The odds ratio (OR) with 95% confidence interval (CI) was evaluated by multilevel logistic regression.

	N	IHM (%)	p (x^2)	OR (95% CI)
Age class (years)			<0.001	
<55	6,986	9.2%		1.00
55-64	5,384	11.0%		1.17 (1.03-1.33)
65-74	6,598	12.2%		1.36 (1.21-1.53)
75-84	4,602	14.6%		1.74 (1.53-1.98)
≥85	1,000	18.9%		2.54 (2.09-3.10)
Sex			0.085	
Male	16,724	12.1%		1.00
Female	7,846	11.3%		0.89 (0.81-0.97)
Underlying liver disease			<0.001	
Unspecified/other	5,955	11.3%		1.00
Liver cancer	2,349	18.7%		1.31 (1.08-1.60)
Alcoholic liver disease	5,402	12.8%		1.19 (1.05-1.36)
Non-alcoholic liver disease	10,864	10.2%		0.86 (0.77-0.96)
Severity of liver disease			<0.001	
Complications mentioned	20,785	10.5%		1.00
Not mentioned	3,785	19.1%		2.31 (2.09-2.57)
Charlson Comorbidity Index			<0.001	
0-1	20,543	10.8%		1.00
2	2,904	17.5%		1.37 (1.16-1.62)
≥ 3	1,123	15.8%		1.30 (1.05-1.59)
Calendar period			0.002	
2001-2005	9,428	12.5%		
2006-2010	7,966	11.9%		0.95 (0.85-1.07)
2011-2015	7,176	10.7%		0.85 (0.76-0.96)

N= number; IHM= in-hospital mortality; OR= odds ratio; CI= confidence intervals.

Table III. Independent association of female sex with in-hospital mortality due to acute oesophageal bleeding in different liver diseases diagnosed according to ICD-9-CM codes.

Liver disease	Population (n)	OR	95% CI	p
Unspecified	5,955	0.89	0.73-1.07	0.22
Liver cancer	2,349	0.84	0.63-1.14	0.26
Alcoholic	5,402	1.21	0.98-1.50	0.074
Non-alcoholic	10,864	0.77	0.66-0.89	<0.001

n= number; OR= odd ratio; CI= confidence intervals.

ceal bleeding ranges from 32 to 80%[7]. Similar to our study, Sharara et al[7] showed that sex was also a risk factor for AOEVB-related IHM. Sato et al[8] investigated risk factors for IHM in a large sample population using a nationwide Japanese database including 9,987 patients with AOEVB. As in our study, comorbidities were assessed with the CCI. The median age for AOEVB was 63 years (68.8% were male), and IHM occurred in 1,676 (16.8%) patients. In the multivariate analysis, IHM was significantly associated with male sex, older age, Child-Pugh class B or C and higher CCI. The authors concluded that despite recent medical advances in the treatment of AOEVB, IHM was as high as 16%, with poor liver function being the most important predictor[8]. Lenzen et al[9] examined risk factors for gastrointestinal bleeding (GIB) in the Emergency Department of a tertiary hospital. More than 45,000 patients were retrospectively evaluated from January 2007 to December 2012. A total of 578 (1.3%) patients presented with GIB, of whom 62.5% were men. Multivariate logistic regression identified older age and male sex as independent predictors of GIB. The authors concluded that patients with acute GIB were aged males and more frequently admitted to the Emergency Department in winter months and during the night[9]. Nationwide trends of AOEVB-related IHM were also evaluated in the USA[10]. The authors analysed the Nationwide Inpatient Sample database from 1988 to 2004 and found that the overall IHM decreased from 18 to 11.5%; when the analysis was adjusted for age, the IHM rate showed an even higher decrease, going from 1,289 per 100,000 to 704 per 100,000 (i.e., almost 46% lower mortality). Multivariate logistic regression analysis showed that male sex, African American race, age, large hospital size, urban location, teaching hospitals, and hospitals located in the North-Eastern USA were independent risk factors for increased mortality[10]. Conversely, studies concerning peptic ulcer bleeding (PUB) showed increased long-term mortality. In a recent observational study comparing consecutive patients admitted with PUB with a matched control cohort from the source population, Laursen et al[11] assessed predictors of mortality by using proportional hazards models and adjustments for CCI. In 455 PUB cases and 2,224 control subjects, the authors found a median survival of 7 and 12 years, respectively, at a median follow-up of 9.7 years. Compared to controls, PUB patients had a higher number of comorbidities, older age, predominantly male sex, anaemia, and smoking habit as predictors of long-term mortality[11]. On the other hand, by developing a score to assess clinical and laboratory parameters and to differentiate variceal and non-variceal bleeding, Pongprasobchai et al[12] identified only 3 risk factors for AOEVB, i.e., previous diagnosis of cirrhosis or signs of chronic liver disease, haematemesis and bloody aspirate drained via nasogastric tube. However, the Pongprasobchai et al[12] study included only 47 patients with AOEVB, 87% of whom were males. In another study, Matei et al[13] evaluated 517 patients, of whom 154 had AOEVB with predominantly male sex (67.5%). Multivariate logistic regression analysis showed that diagnosis of cirrhosis, history of previous AOEVB, ascites, thrombocytopenia, elevated INR and elevated bilirubin levels were independently associated with AOEVB[13]. Alharbi et al[14] investigated 2,020 patients, of whom 215 had AOEVB, and showed a mean age of 58±12.3 years with almost 30% of patients being female. AOEVB was associated with a history of liver disease, excessive alcohol intake, haematemesis, haematochezia, and stigmata of chronic liver disease[14]. Lung et al[15] evaluated 888 cirrhotic patients hospitalized for AOEVB and examined the impact of diabetes mellitus (DM) and chronic kidney disease (CKD) on mortality. All-cause mortality at 42 days and one year were 21.3 and 45%, respectively. Females with DM and CKD had higher hazard ratios for all-cause mortality at 42 days and one year than males (4.03 and 2.84 *vs.* 2.93 and 2.42, respectively)[15]. Liu et al[16] evaluated clinical

factors associated with mortality in more than 150,000 cirrhotic patients with previous AEBV and found that age, female sex, CCI score > 1, and hospitals with medium to high or very high doctor service volume were independently associated with IHM and 5-year mortality. In this 15-year nationwide population-based cohort study, the female sex-related hazard ratio was 1.263, as was shown by multivariate analysis[16]. The different results shown by several studies published to date could be attributed to different study designs, patient selection bias and, finally, to the "female paradox" observed mainly in subjects with alcoholic liver disease, with female subjects being more susceptible to alcohol-related liver damage. Recent data indicate an increasing dose-dependent relative risk of developing alcohol-induced liver disease for both men and women. However, women have a significantly higher relative risk of alcohol-related liver disease than men for any level of alcohol intake[17]. Hepatic damage could be even worse in postmenopausal women. It has been suggested that a reduced response to oestradiol could contribute to a greater progression of hepatic fibrosis and hepatocellular carcinoma in men and postmenopausal women[18]. Using an animal model, Naugler et al[19] demonstrated that oestrogens, at concentrations present in females but not in males, suppress IL-6 production by Kupffer cells, thus inhibiting liver fibrosis and carcinogenesis[19]. Serum IL-6 concentrations were found to be increased under conditions such as alcoholic hepatitis, HBV and HCV infections and steatohepatitis responsible for chronic liver inflammation[20]. Hepatic fibrosis progression due to HBV and HCV infections appears to be slower in females than in males[21,22], and menopause is associated with hepatic fibrosis progression, underlying the protective abilities of oestrogens against progression to chronic liver disease[23]. The oestrogen-mediated mechanisms may be taken into account to explain our results, which show a lower risk of AEAB-related IHM in women with non-alcoholic liver disease. In contrast, women appear to be more susceptible to alcohol damage. In fact, compared to men, women show lower first-pass alcohol metabolism (due to lower gastric alcohol dehydrogenase activity), slower gastric emptying of alcohol and, last but not least, higher hepatic oxidation[24]. These pharmacokinetic features may increase the vulnerability of women to the effects of ethanol. Very recently, Italian authors tested the hypothesis of an additive interaction due to the simultaneous presence of HBV, HCV and alcohol intake on the risk of developing cirrhosis. They found an additive interaction in females but not in males[25]. Our study has several limitations, mainly due to its retrospective design and utilization of administrative data based on ICD-9-CM codes:

The national database does not include information on the acuity of illness or the time from the onset of symptoms to the presentation, haemodynamic stability, or medications, possibly contributing to the severity of presentation (e.g., anticoagulants, antiplatelets). Similarly, we did not have data on laboratory values, biomarkers[26] and disease progression[27] used in the risk assessment of AOEVB patients.

Administrative comorbidity data likely underestimate the true prevalence of comorbid conditions.

Mortality assessment is limited to all-cause hospital mortality; we could not evaluate post-discharge mortality because of the inability to determine whether deaths were related to variceal haemorrhage or other diseases or hospital-acquired events.

However, the significant strength of this study is its large sample size; additionally, it is based on the national hospital database, which was used recently for investigating hard outcomes on a national basis and enabled a representative cross-sectional view throughout the country of Italy [28,29].

Conclusions

AOEVB-related IHM is decreasing and in most cases involves aged patients with different liver diseases and comorbidities. Although men remain at high risk, female sex appears to be protective only in those with non-alcoholic liver disease, whereas the risk is increased in females with alcoholic liver disease. Overall, the risk of AOEVB and related IHM is increased in any patient with multiple comorbidities.

Conflict of Interest

All authors had no conflicts of interest related to this paper. The authors declare that there are no potential conflicts of interest that are directly or indirectly related to the data presented in the paper.

Author Contributions

The authors made substantial contributions to conception and design, acquisition of the data, or analysis and interpretation of the data; The authors drafted the article and revised the article critically for important intellectual content; The authors gave final approval of the version to be published and agreed to be accountable for all aspects of the

work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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