



Cirrhosis Due to Alcohol-Related Liver Disease Hospitalizations in Belgrade, Serbia: A 10-Year Retrospective

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Abstract

Background: Cirrhosis due to alcohol-related liver disease (ALD cirrhosis) is a significant burden to health systems worldwide. We aimed to determine the trends in hospitalization frequency due to ALD cirrhosis and to analyze their characteristics.

Methods: This cross-sectional study used data from the Institute of Public Health of Belgrade database, and included all hospitalization reports which contained code K70.3 (Cirrhosis hepatitis alcoholica) as the primary diagnosis, including re-hospitalizations, on the territory of Belgrade, between January 2009 and December 2018.

Results: A total of 4644 patients with ALD cirrhosis were hospitalized (male: 4154, 89.45%), with a mean age of 58.83 ± 10.02 years. During the 2009-2018 decade, no difference in the number of ALD cirrhosis hospitalizations in subsequent years was observed. Men more commonly developed esophageal and gastric varices with bleeding compared to women ($P=0.037$), while women developed acute-on-chronic liver failure (ACLF) almost two-times more often compared to men ($P<0.001$). Patients with hepatocellular carcinoma were significantly older ($P<0.001$), while those who developed ascites and splenomegaly were significantly younger compared to those who did not ($P<0.001$ and $P=0.04$, respectively). Altogether, complications of portal hypertension were registered and reported with very low frequency, and therefore do not represent actual frequencies of these conditions. The median duration of hospital stay was 9 days (range 0-243). Patients in whom lethal outcome occurred during the hospitalization were significantly older, and more commonly developed chronic renal failure.

Conclusion: These data offer an important insight into the ALD cirrhosis-related hospitalizations while drawing attention to inadequate coding as an important public health issue at the same time.

Keywords: Alcohol-related liver disease; Cirrhosis; Hospitalization; Public health



Introduction

Cirrhosis due to alcohol-related liver disease (ALD cirrhosis) occurs due to excessive and chronic alcohol use. The degree of liver damage depends mainly on the duration, amount, and pattern of alcohol consumption, genetic susceptibility, and associated health conditions (1, 2). The threshold of alcohol consumption at which the risk for liver cirrhosis development emerges is debatable. However, if alcohol is consumed, intake should be limited to 30 g of ethanol per day in men, and 20 g per day in women (3). According to the WHO Global status report on alcohol and health, around 2.3 billion people worldwide are current drinkers, with the highest prevalence of current drinkers in the European Region (59.9%) (4). The harmful alcohol use resulted in an estimated 5.3% of all deaths globally in 2016, while the contribution of alcohol to digestive diseases was also highest in Europe, where 30.5% of all digestive diseases deaths (most commonly liver cirrhosis) were due to alcohol consumption (4). Given the fact that ALD is widely underreported and due to the inadequate disease registries, the exact prevalence of ALD in our country is unknown. However, regarding health consequences of harmful alcohol consumption, the WHO estimates that age-standardized death-rates due to liver cirrhosis are 13 per 100000 population in males, and 2.5 per 100000 population in females. Additionally, in those with liver cirrhosis alcohol-attributable fraction is estimated to be 77.3% in men, and 57.3% in women (4).

The majority of ALD cirrhosis complications develop as a result of portal hypertension. The natural history of the disease is characterized by a long asymptomatic, "compensated" phase, followed by a progressive, "decompensated" phase (5). Decompensated cirrhosis is defined as liver failure in patients with end-stage liver disease, which can manifest itself through a broad spectrum of clinical conditions including icterus, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato-renal and hepato-pulmonary

syndrome, and varicose bleeding. Since more than 60% of patients with liver cirrhosis during the 10-year course of the compensated phase develop ascites, it is considered to be the most common clinical sign of decompensated cirrhosis, and usually the reason for seeking medical attention, irrespective of the cirrhosis etiology (5-7). On the other hand, the most significant complication of portal hypertension is life-threatening bleeding from gastrointestinal varices, which frequently requires intensive-care unit (ICU) admission, and is associated with significant in-hospital mortality (7-9). During the previous years, hospitalization trends due to ALD cirrhosis are increasing (10-12). Additionally, in ICU patients cirrhosis is associated with higher mortality and increased medical expenditures, especially when co-existent with alcohol dependence and previous multiple cirrhosis-related admissions (13, 14). We aimed to determine the trends in hospitalization due to ALD cirrhosis, to analyze their clinical characteristics, together with the effect of demographic and clinical characteristics of ALD cirrhosis patients on length of stay (LOS), level of administered hospital care, and treatment outcome.

Methods

Sample and data collection

For the purpose of this cross-sectional study, data were collected from the Institute of Public Health of Belgrade database, which contains data regarding public health services provided in the city of Belgrade. All hospitalization reports which included adult subjects, and contained code K70.3 (Cirrhosis hepatitis alcoholica) as the primary diagnosis (re-hospitalizations included), on the territory of Belgrade between January 2009 and December 2018, were extracted for further analyses. Codes were based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes. The presence of codes addressing ALD cirrhosis-

related conditions (K76.6 Hypertensio portalis, I85.0 Varices oesophagi cum haemorrhagia, I85.9 Varices oesophagi sine haemorrhagia, R18 Ascites, G92 Encephalopathia toxica, K65.0 Peritonitis acuta, K76.6 Syndroma hepatorenale, D73.1 and R16.1 Hypersplenismus, Splenomegalia, D69.5 and D69.6 Thrombocytopenia, non specificata; Thrombocytopenia secundaria, K72.1 Insufficiencia hepatis chronica, K72.0 Insufficiencia hepatis acuta et subacuta, C22.0 Carcinoma hepatocellulare), and other co-existing medical conditions (I10 Hypertensio arterialis, E10 and E11 Diabetes mellitus ab insulin dependens, Diabetes mellitus ad insulin independens, N18 Morbus renalis chronicus) was analyzed in collected hospitalization reports as well. Patients hospitalized due to liver cirrhosis of other etiology, and patients with ALD cirrhosis hospitalized due to unrelated disorders were excluded. Given the fact that all data analyzed during this research are publicly available, there was no need for obtaining Institutional Ethics committee approval.

Variables and definitions

The following independent variables were taken into account during the data analyses: age, sex, presence of ALD cirrhosis-related conditions, and the aforementioned co-existing medical conditions. The length of stay, level of hospital care administered, and treatment outcome were considered as dependent variables. There were three categories of hospital wards, depending on the administered level of medical care (level of care 1, 2, and 3). Level of care 1 was defined as a hospital ward with several common rooms, with on average 10 hospital beds (ranging from 3 to 15) and a shared bathroom. Level of care 2 was defined as a hospital ward with hospital rooms containing up to three hospital beds, an internal bathroom, and increased patient surveillance. Level of care 3 was defined as an equivalent to

the ICU, regardless of its organization. Treatment outcome was considered unfavorable if the hospitalization report contained the code referring to “the patient’s death”, and favorable if that was not the case.

Statistical analysis

For continuous variables, mean and standard deviation or median and range were calculated depending on the normality of data distribution. Categorical data were presented as frequencies. The normality of distribution was examined both graphically and numerically. Difference in hospitalization trends was determined using Chi-square test. Categorical variables were analyzed by Chi-square or Fisher’s exact test, where appropriate. Student’s t-test and ANOVA were used for normally distributed continuous variables and Mann-Whitney-Wilcoxon test for non-normally distributed continuous variables. All tests were two-tailed and P -value <0.05 indicated statistical significance. Statistical analysis was performed using Easy R (EZR) software.

Results

During the study period, a total of 4644 hospital admissions due to ALD cirrhosis were noted, out of which 4154 (89.45%) included male, and 490 (10.55%) female subjects. The mean age was 58.83 years ± 10.02 . On admission, women were significantly older compared to men (59.96 ± 10.82 *vs.* 58.72 ± 9.84 ; $P=0.016$).

During the 2009-2018 decade, no statistically significant difference in the number of ALD cirrhosis hospitalizations in subsequent years (pooled for all age groups) was noted, with no difference in hospitalization trends regarding sex either (Fig. 1).

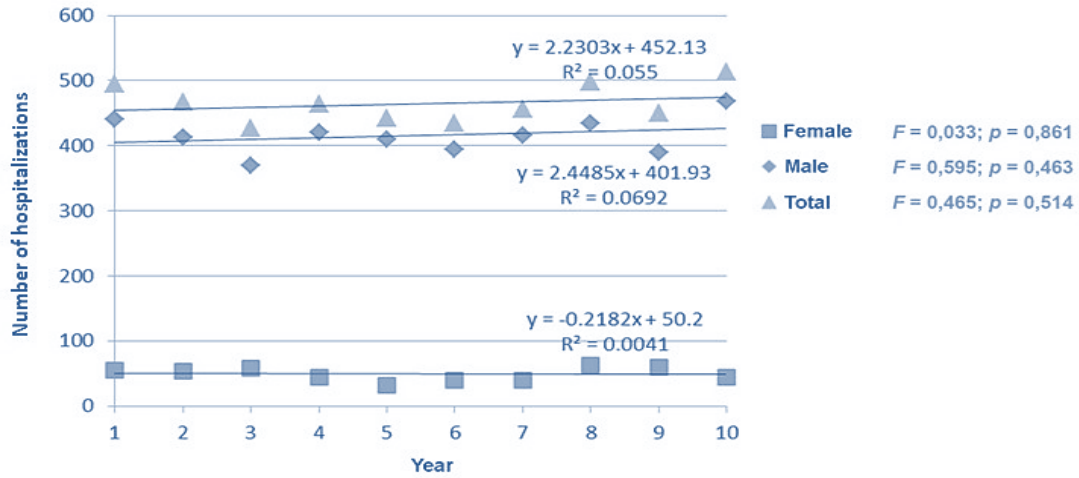


Fig. 1: Alcoholic cirrhosis hospitalizations by gender in consecutive years in Belgrade (January 2009 – December 2018)

The highest frequency of hospitalization was recorded in January, while the lowest was noted in December, which was of statistical significance ($X^2=96.222$; $P<0.001$). No statistically significant

difference in the frequency of hospitalization between the sexes was noted during the observed period ($X^2=13.637$; $P=0.254$) (Fig. 2).

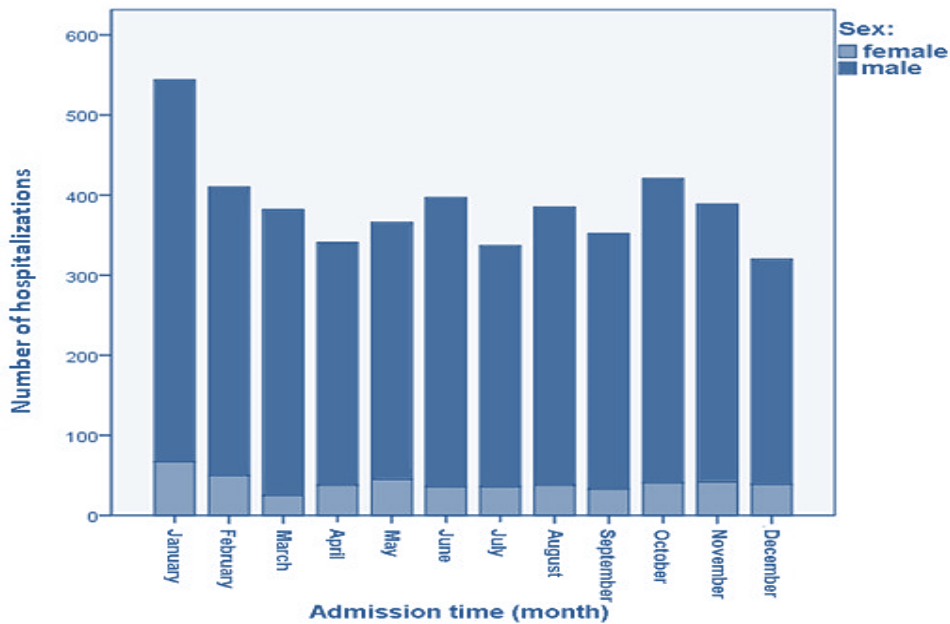


Fig. 2: Monthly frequency of hospitalization of patients with alcoholic cirrhosis (January 2009 - December 2018)

After evaluating the effect of patients' sex and age on the prevalence of cirrhosis-associated conditions, we observed that men more commonly developed bleeding varices compared to

women ($P=0.037$), while women developed acute-on-chronic liver failure (ACLF) almost two-times more often compared to men ($P<0.001$). The mean age of patients with portal

hypertension and hepatocellular carcinoma was significantly higher, compared to those without these conditions ($P<0.001$ and $P<0.001$, respectively). On the other hand, patients who developed ascites and splenomegaly were significantly

younger compared to those who did not ($P<0.001$ and $P=0.04$, respectively). Differences in frequency of cirrhosis-associated conditions with respect to patients' sex and age are presented in detail in Table 1.

Table 1: Prevalence of cirrhosis-associated conditions and differences in patients' demographic characteristics

<i>Cirrhosis-associated conditions (n, %)</i>	<i>Total (n, %)</i>	<i>Sex (n, %)</i>		<i>p</i>	<i>Age (mean±SD)</i>		<i>p</i>
		Male	Female				
Portal hypertension							
Yes	4218 (90.83)	3796 (90.7)	449 (91.6)	0.514	58.99	10.09	<0.001
No	426 (9.17)	385 (9.3)	41 (8.4)		57.23	9.21	
Esophageal and gastric varices without bleeding							
Yes	753 (16.21)	679 (16.3)	74 (15.1)	0.48	58.75	10.29	0.799
No	3891 (83.79)	3475 (83.7)	416 (84.9)		58.85	9.97	
Esophageal and gastric varices with bleeding							
Yes	729 (15.7)	668 (16.1)	61 (12.4)	0.037	58.44	9.77	0.253
No	3915 (84.3)	3486 (83.9)	429 (87.6)		58.9	10.07	
Ascites							
Yes	3975 (85.59)	3568 (85.9)	407 (83.1)	0.091	58.42	10.17	<0.001
No	669 (14.41)	586 (14.1)	83 (16.9)		61.27	8.7	
Hepatic encephalopathy							
Yes	325 (7)	290 (7)	35 (7.1)	0.894	59.17	10.28	0.524
No	4319 (93)	3864 (93)	455 (92.9)		58.81	10	
Spontaneous bacterial peritonitis							
Yes	17 (0.37)	14 (0.3)	3 (0.6)	0.34	58.41	8.25	0.861
No	4627 (99.63)	4140 (99.7)	487 (99.4)		58.83	10.03	
Hepato-renal syndrome							
Yes	93 (2)	82 (2)	11 (2.2)	0.686	60.34	10.97	0.143
No	4551 (98)	4072 (98)	479 (97.8)		58.8	10	
Splenomegaly							
Yes	137 (2.95)	117 (2.8)	20 (4.1)	0.118	57.13	9.58	0.04
No	4507 (97.05)	4037 (97.2)	470 (95.9)		58.88	10.03	
Thrombocytopenia							
Yes	98 (2.11)	84 (2)	14 (2.9)	0.224	58.23	9.76	0.548
No	4546 (97.89)	4070 (98)	476 (97.1)		58.84	10.03	
Chronic hepatic failure							
Yes	4283 (92.23)	3830 (92.2)	453 (92.4)	0.846	58.02	10.35	0.108
No	361 (7.77)	324 (7.8)	37 (7.6)		58.9	9.99	
Acute-on-chronic liver failure							
Yes	222 (4.78)	182 (4.4)	40 (8.2)	<0.001	58.17	10.11	0.31
No	4422 (95.22)	3972 (95.6)	450 (91.8)		58.87	10.02	
Hepatocellular carcinoma							
Yes	44 (0.95)	39 (0.9)	5 (1)	0.86	64.86	8.69	<0.001
No	4600 (99.05)	4115 (99.1)	485 (99)		58.77	10.02	

The median LOS was 9 days (range 0-243). The difference in median LOS concerning age groups was statistically significant ($P=0.001$). The difference in median LOS was statistically significant between patients belonging to the age groups 31-50 and 50-70 years ($P<0.001$). No statistically significant difference was found between the

other age groups. Patients with a concomitant diagnosis of arterial hypertension (HTA) experienced significantly longer hospitalization ($P=0.03$). The effect of patients' characteristics and co-morbidities on the duration of hospitalization is presented in detail in Table 2.

Table 2: The effect of patients' demographic characteristics and co-morbidities on the length of stay

<i>Variable</i>	<i>Length of stay</i>		
	Median	Range	<i>P</i>
Sex			
Male	9	0-96	0.07
Female	9	0-243	
Age groups			
18-30	8	1-53	0.001
31-50	10	0-243	
51-70	9	0-148	
>71	10	0-185	
Co-morbidities			
Diabetes mellitus (n, %)			
Yes	9	0-96	0.056
No	9	0-243	
Arterial hypertension (n, %)			
Yes	10	1-185	0.03
No	9	0-243	
Chronic renal failure (n, %)			
Yes	10	0-53	0.39
No	9	0-243	

Once hospitalized, the majority of patients were treated in care level 1 hospital wards (3680, 79.4%). A total of 316 (6.8%) patients were treated in care level 2, and 648 patients (13.95%) in care level 3 hospital wards. Statistically significant difference was noted among the mean age of patients hospitalized in care level 1, 2, and 3 hospital wards ($P=0.02$), with no significant mean age differences when the three groups were compared to one another separately ($P>0.05$). A statistically significant difference in frequency of both diabetes mellitus (DM) and HTA in relation to the level of hospital care was observed as well ($P=0.02$ and $P<0.001$, respectively) (Table 3).

Unfavorable outcome occurred in 15.82% ($n=735$) of hospitalized patients with ALD cirrhosis. Patients in whom lethal outcome occurred during the hospitalization were significantly older, compared to those who experienced favorable outcome ($P<0.001$). The frequency of HTA was significantly lower in those with unfavorable outcome ($P=0.04$), while the frequency of chronic renal failure was significantly higher in the same group of patients ($P<0.001$). Details regarding the effect of patients' demographic characteristics and co-morbidities on the treatment outcome are presented in detail in Table 4.

Table 3: The effect of patients' demographic characteristics and co-morbidities on the level of hospital care

<i>Variable</i>	<i>Level of hospital care (n,%)</i>			<i>p</i>
	1	2	3	
Age (mean±SD)	59.03±9.93	57.93±9.93	58.12±10.54	0.02
Sex (n,%)				
Male	3297 (89.6)	284 (89.9)	573 (88.4)	0.65
Female	383 (10.4)	32 (10.1)	75 (11.6)	
Co-morbidities				
Diabetes mellitus (n, %)				
Yes	474 (12.9)	30 (9.5)	63 (9.7)	0.02
No	3206 (87.1)	286 (90.5)	585 (90.3)	
Arterial hypertension (n, %)				
Yes	480 (13)	26 (8.2)	31 (4.8)	<0.001
No	3200 (87)	290 (91.8)	617 (95.2)	
Chronic renal failure (n, %)				
Yes	118 (3.2)	9 (2.8)	13 (2)	0.25
No	3562 (96.8)	307 (97.2)	635 (98)	

Table 4: The effect of patients' demographic characteristics and co-morbidities on the treatment outcome

<i>Variable</i>	<i>Outcome</i>		<i>p</i>
	Favorable	Unfavorable	
Age (mean±SD)	58.52±10.04	60.51±9.78	<0.001
Sex (n, %)			
Male	3503 (84.3)	651 (15.7)	0.399
Female	406 (82.9)	84 (17.1)	
Co-morbidities			
Diabetes mellitus (n, %)			
Yes	481 (84.8)	86 (15.2)	0.646
No	3428 (84.1)	649 (15.9)	
Arterial hypertension (n, %)			
Yes	468 (87.2)	69 (12.8)	0.044
No	3441 (83.8)	666 (16.2)	
Chronic renal failure (n, %)			
Yes	90 (64.3)	50 (35.7)	<0.001
No	3819 (84.8)	685 (15.2)	

Discussion

In this cross-sectional, registry-based study we observed no difference in hospitalization trends due to ALD cirrhosis during a 10-year period in Belgrade, Serbia. The provided results suggest the underestimation of ALD cirrhosis-related conditions prevalence, which is identified as a significant public health issue. We observed that younger age is associated with longer hospital stay, while older age is associated with unfavora-

ble outcome. Presence of co-morbidities is more common in those treated in lower levels of hospital care.

In our study, the mean age of ALD cirrhosis patients was 58.83 years ±10.02, which is higher compared to some other similar studies (11, 12, 15). Additionally, in our study, the majority of subjects were men, while women were significantly older compared to men (59.96±10.82 *vs.* 58.72±9.84; *P*=0.016), which is in concordance with the results reported already (11).

Interestingly, female subjects in our study were almost a decade older compared Whitfielda et al. (59.96 ± 10.82 vs. 50.1 ± 9.6) (16). The possible explanation for the significant discrepancy is that women deny alcohol consumption, due to the unwavering social stigma present in our country, and therefore postpone seeking medical care (17). During the observed 10-year period no difference in trends of hospitalization due to ALD cirrhosis per year was observed in our study, which is in contrast to several other studies, which reported a significant increase in hospitalization rates due to ALD cirrhosis, especially in men (10-12).

When it comes to complications of portal hypertension, in our study ascites was the one reported with the highest frequency (85.59%), which is slightly higher, but consistent with the data reported in the Genome ALC study (16). The rest of the complications were reported with lesser frequency compared to the other studies. For instance, esophageal and gastric varices with and without bleeding were reported in 16.21% and 15.7% of subjects respectively, while the reported frequency of esophageal varices and variceal bleeding was as high as 93% and 30.19%, respectively, in the cohort of patients (18). Similarly, the reported frequency of overt hepatic encephalopathy in ALD cirrhosis patients is more than 30%, while the reported incidence of spontaneous bacterial peritonitis, hepato-renal syndrome, and the prevalence of splenomegaly is up to 14%, 12%, and 55%, respectively (16, 19-21). In our study the aforementioned conditions were reported in only 7%, 0.4%, 2%, and 3% of all hospital admissions, respectively. Moreover, the estimated prevalence of moderate and severe thrombocytopenia in patients with ALD cirrhosis is 13% and 1%, respectively (22), while in our study, thrombocytopenia was reported in only 2.1% of all admissions. ACLF was also reported with a significantly lower frequency compared to a prospective study by Moreau *et al.* (4.78% vs. 30.9%). They observed that the patients with ACLF on enrollment are younger, with no differences regarding gender (23). Our results show no differences in respect with age, but we did observe that ACLF was almost two times more

common in women. At this point, it is abundantly clear that our results cannot represent the actual frequencies of the aforementioned conditions in ALD cirrhosis patients. The prominent discrepancy between our and the results of the other studies could be explained by inadequate coding of associated conditions, as well as the fact that the cirrhosis-unrelated conditions are commonly unintentionally omitted from discharge papers. Furthermore, one should bear in mind the economic setting and healthcare structure in which the research was conducted. For example, healthcare systems in developing countries are facing numerous challenges, some of which are reflected in the lack of implementation of a unique healthcare information system, which would facilitate adequate and uniform coding (24).

The median LOS was 9 days (range 0-243), which is significantly longer compared to the other similar American studies (10, 25), while at the same time slightly shorter compared to the European studies (11). We found that the difference in median LOS in respect to the age groups was statistically significant, indicating that younger subjects had a longer hospital stay. Similarly, Marinho et al. reported an earlier age of admission trend in ALD cirrhosis patients (11). The explanation for our results could be the fact that the first episode of decompensation occurs earlier, and at the same time requires a thorough diagnostic work-up, and a subsequent longer hospital stay.

We observed that subjects treated in lower levels of hospital care more commonly had DM and HTA. Because of the way data were collected, we were only able to stratify patients based on the level of hospital care assigned upon admission. During treatment, certainly a significant proportion of patients required a transfer to either a higher or lower level of hospital care, depending on the clinical course of the disease. Therefore, we were not able to determine if the presence of the aforementioned co-morbidities might have influenced the treatment course or the transfer to a different care unit. Our results could be explained by the fact that patients with co-morbidities usually have regular medical check-

ups, which would lead to earlier detection of other conditions and a referral to the specialist care at the point when severe manifestations of the disease have not developed yet.

Patients in whom lethal outcome occurred during the hospitalization were significantly older. The frequency of HTA was significantly lower in those with unfavorable outcome, while the frequency of chronic renal failure was significantly higher in the same group of patients. Besides previously mentioned inadequate coding, we are lacking an explanation for the lower frequency of HTA in cases of an unfavorable outcome, while the association of chronic kidney failure with worse outcome in cirrhotic patients is well established (26).

Limitations of the study

Studies derived from large claims databases, including ours, have several limitations, and therefore the presented results should be interpreted carefully. Firstly, the Institute of Public Health of Belgrade, as any other similar register, records data per hospitalization, and not per individual patient. Given the fact that patients with ALD cirrhosis commonly require repeated hospital admissions due to various reasons, we are aware of the significant proportion of re-hospitalizations included. Additionally, given the cross-sectional nature of our study, with no data regarding follow-up, neither longitudinal nor cause-effect analysis was possible. Nevertheless, since this is the first Southern-European study that aimed to evaluate major aspects of ALD cirrhosis hospitalizations, these results provide valuable information regarding several public health issues. We are hoping that this study is only a springboard for future research of this kind, which would allow data comparison, and therefore a more comprehensive view of all of the ALD aspects. It is indisputable that ALD presents a significant burden to health systems worldwide, and even though it is a leading cause of cirrhosis, unfortunately it is still considered as an “orphan disease” of hepatology, which commonly results in inadequate disease management. Therefore, we made an effort to draw attention

to the frequently overlooked issues present in everyday practice, which is a first step in improving the treatment of this specific group of patients.

Conclusion

The male subjects comprise the majority of ALD cirrhosis hospitalizations. We observed no difference in trends of hospitalization due to ALD cirrhosis per year. Complications of portal hypertension were registered and reported with low frequency, which is probably the result of unintentional inadequate disease coding on discharge documentation and does not represent the actual frequencies of these conditions. Age and presence of co-morbidities affect both length of stay and hospitalization outcome. Even though our results must be interpreted with caution, our study offers an important insight into the ALD cirrhosis-related hospitalizations, while addressing an important public health issue at the same time.

Journalism Ethics considerations

Ethical considerations including plagiarism, data fabrication and/or falsification, misconduct, double publication, and/or submission have been completely observed.

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Conflict of interest

The authors have no conflict of interest to declare.

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