The undertreatment of alcohol-related liver diseases among people with alcohol use disorder

E. SCAFATO¹, F. CAPUTO², V. PATUSSI³, P. BALBINOT⁴, G. ADDOLORATO⁵, G. TESTINO⁶

Abstract. - Harmful and hazardous alcohol consumption is one of the most significant public health problems in Italy and Europe. Habitual excessive consumption and occasional excessive consumption, known as binge drinking, are the two main risk behaviours related to alcohol. Harmful drinking and alcohol dependence have strong social repercussions in terms of their social and economic impact and contribution to productivity losses. In addition, the terms alcohol abuse and alcohol dependence have been recently substituted by the only term of alcohol use disorder (AUD). The issues presented in this review demonstrate that excessive alcohol consumption is a growing public health concern and an appropriate national action plan is needed to increase the prevention of harmful and hazardous consumption and encourage patients to seek healthcare. To date, the main problem is the under-treatment of the population at risk, manifested as the time-lag between the onset of AUD and the first clinical detection. In order to address this, the Screening, Brief Intervention, and Referral to Treatment (SBIRT) strategy has been shared across countries in Europe and is supported by a Systematic Review of Reviews on SBIRT in primary healthcare. Unfortunately, there are still obstacles in the implementation of this approach. The main problem would appear to be general practitioners' difficulty in carrying out accurate and widespread screening, because they may minimize the problem. A more concerted effort in the training of healthcare professionals could address this by enabling the

creation of renewed networks for the early identification of harmful and hazardous drinkers. These networks could prevent the occurrence of avoidable alcohol-related conditions, such as alcohol-related liver disease (ALD), while allowing for the timely implementation of evidence-based brief interventions.

Key Words:

Alcohol-related liver disease, Undertreatment, Alcohol use disorder.

Harmful and Hazardous Drinkers

Alcohol-use disorders (AUD) cover a wide range of health problems, including hazardous and harmful drinking and alcohol dependence, and are recognised within the following international disease classification systems: ICD-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Harmful and hazardous alcohol use is one of the most relevant public health problems in Italy and the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) lists alcohol as the fourth highest risk factor of illness and mortality in Central and Eastern Europe¹. Harmful use of alcohol is one of the main factors contributing to premature deaths and disability and has a major impact on public health. The harmful use of

¹National Observatory on Alcohol, National Institute of Health, Rome, Italy

²Department of Internal Medicine, SS Annunziata Hospital, Cento (Ferrara), University of Ferrara, Italy ³Department of Alcohology, AOU Firenze, Florence, Italy

⁴SC Unit of Addiction and Hepatology, Ligurian Alcohologic Regional Centre, ASL3 Liguria c/o Ospedale Policlinico San Martino, Genoa, Italy

⁵Alcohol Use Disorder Unit, Division of Internal Medicine, Gastroenterology and Hepatology Unit, Catholic University of Rome, A. Gemelli Hospital, Rome, Italy and Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy

⁶SC Unit of Addiction and Hepatology, Ligurian Alcohologic Regional Centre, ASL3 Liguria c/o Ospedale Policlinico San Martino, Genoa, Italy

alcohol encompasses several aspects of drinking, such as the volume of alcohol drunk over time, the pattern of drinking that includes occasional or regular drinking to intoxication, and the drinking context if it increases the public health risk.

According to ICD-10, harmful drinking is a way of persistent hazardous alcohol consumption that results in physical or psychological harm to the body; consumers that exceeded the limit of 40 grams/day of pure alcohol for females, and 60 g/day for males [more than 3 Units of Alcohol and more than 5 Units of Alcohol respectively, where 1 Unit of Alcoholis equivalent to the Italian standard of 12 g of alcohol, and is very close to the European RARHA (Joint Action Reducing Alcohol Related Harm) average of 11 grams] are considered harmful drinkers. Harmful drinking was introduced in ICD-10 as a diagnostic term.

The World Health Organization (WHO) definition of hazardous drinking is not diagnostic as it refers to a level of consumption or pattern of drinking that puts individuals at risk for adverse health events. Increasing emphasis has been placed on the detection and treatment of hazardous and harmful drinking disorders, particularly among patients in primary care settings, in order to reduce the risk of various diseases (e.g., infectious and chronic diseases, liver diseases, and cancer) and of premature deaths and disabilities due to cardiovascular diseases. Cancer, liver cirrhosis, and accidents account for more than the 85% of all the alcohol-related conditions' impact on society, with the rest attributable to injuries, aggression, suicide, and violence. Exposure of the foetus to alcohol during the pregnancy also increases the risk of birth defects and cognitive deficits. The primary goal of intervention is to facilitate a reduction in alcohol intake to non-hazardous levels, and thereby lessen the risk of harmful consequences.

The most recent guidelines stress the importance of not exceeding on a daily basis specified quantity of alcoholic standard units that are defined as low-risk drinking limits, while emphasizing that below them risks still exist². In Italy, the National Guidelines recommend that males not exceed a daily consumption of 2 standard Alcohol Unit (AU), women and elderly people limit themselves to a daily consumption of 1 AU, and young people under the legal age of 18 years to completely abstain from drinking. A second recommendation is not to drink following the modality of binge drinking defined as drinking more than 5-6 alcoholic drinks (on average more than 60 grams of alcohol) in one occasion over a very

short period of time³. Recent data confirmed that binge drinking among adolescents represents a risk factor for the development of AUD⁴.

It is therefore important to screen and monitoring an individual's alcohol consumption, in order to identify regular consumption potentially exceeding the low-risk drinking guidelines or to quantify it as binge drinking. The Italian Observatory on Alcohol at the National Institute of Health regularly reports the trends of a series of standardized indicators that can be crucial in orienting policy-makers towards setting adequate alcohol policies aimed at the prevention of AUD. A special focus of the national monitoring system SIS-MA (http://www.epicentro.iss.it/alcol/SismaMonitoraggio) is to identify the magnitude and yearly trends of alcohol use in Italy among under 18 year olds consuming any alcoholic drink that should be avoided by law and the guidelines recommendation (any type of consumption, even occasional, is considered to be at risk)5. For adult woman and over 65s, the suggested daily consumption limit of 1 Alcohol Unit represents an indicator for orienting national and regional prevention plans and strategies that include a specific target. There is also a gender-based approach aiming at monitoring and reducing the daily consumption for adult men who exceed 2 Alcohol Units per day¹.

For 2017 (the most recent year with available data formally reported to the Parliament by the Minister of Health), 14.8% of males and 5.9% of females aged 11+ declared having exceeded the national low-risk daily guidelines of 2 AU and 1 AU respectively; this estimate suggests that at least 5,600,000 individuals are considered hazardous drinkers, according to this indicator. This estimate also includes the over 65s who exceeded 1 AU and underaged people (11-17 years old) who consumed any quantity of alcoholic beverages. The highest percentage (M=47.0%; F=34.5%) was reported among adolescents for both sexes, as well as for the over 65s (M=35.0%; F=8.0%)¹.

There is an urgent need to prevent and minimize alcohol use by minors, children, and adolescents until they reach the legal age for drinking, in order to not only curb "alcohol epidemics" among young people as a main cause of death, but also to create new generations less harmed by alcohol use and its consequences.

Policy goals for children and adolescents below the legal age limit for the purchase of alcohol include:

- delaying the age of the first use of alcohol;
- · reducing and minimizing amounts of alco-

hol consumed among adolescents who may drink:

reducing harm suffered by children in families with alcohol problems.

A number of indicators have been suggested to monitor alcohol risk⁶. One of the key characteristics of hazardous drinking is the presence of heavy drinking occasions. Heavy episodic drinking (also called binge drinking or risky single-occasion drinking) refers to drink with the aim to achieve alcohol intoxication. The WHO define binge drinking as the proportion of adult drinkers (15+ year old) who have had at least 60 grams or more of pure alcohol (5-6 AU) in at least one occasion in the past 30 days. In Italy this indicator is expressed by the number of 15+ year old drinkers who consumed more than 5-6 alcohol units on one occasion during the last 12 months. Binge drinking has been subject to monitoring in Italy by ISS since 2000 through a multipurpose survey on households. In 2016, the proportion of consumers (over 11 years old) who claimed to have drunk 6 or more glasses of alcohol on one occasion at least once in the last 12 months was 11.2% among men and 3.7% among women, corresponding to four million binge drinkers. The binge drinker percentages increase among teenagers and reach their maximum value between 18-24 years old (M = 21.8%, F = 11.7%), and then, it decreases again in the older population¹.

Harmful and hazardous drinking and binge drinking are the main risk behaviours related to alcohol. These two consumption indicators can be reported separately or in combination, following the official reporting of the national monitoring system SISMA set by Law 125/2001⁷.

Consumers who admitted to binge drinking at least once in the last year numbered 11.2% for males and 3.7% for female, suggesting there are 3,700,000 of 11+ year old binge drinkers with an increased trend between 2007 and 2016 among women. When the two indicators were analysed in combination, in 2016 the prevalence of consumers at risk was estimated as 23.2% for men and of 9.1% for women aged over 11, for a total of 8,600,000 individuals $(M = 6,100,000, F = 2,500,000)^{1}$. The most at-risk population groups are the 16-17-year-old and the 65-75-year-old age groups. About 800,000 minors and 2,700,000 over 65s are at a higher risk for alcohol-related diseases and problems, potentially due to poor knowledge or awareness about alcohol impact on health1. Hazardous drinkers need to be identified early and informed about the consequences of alcohol consumption, as they represent the target population for any kind of brief intervention.

Table I. Prevalence in 2016 of consumers at risk aged 11+1.

Consumers at risk (aged 11+)		
	Men	Women
Prevalence (%) Number of people Total	23.2% 6,100,000 8,600,000	9.1% 2,500,000

Diagnosis Delay and Undertreatment Problem

Diagnosing and identifying a population with alcohol-related problems is still being developed. The current term used to label pathological alcohol consumption is AUD, which includes both alcohol abuse and alcohol dependence classified on the basis of the number of DSM-V positive criteria8. In the past, the most used classification was from the DSM-IV (published in 1994), which did not have a diagnosis of "alcoholism" but instead described two distinct disorders - alcohol abuse and alcohol dependence – with specific criteria for each diagnosis. The DSM-V, which is the current reference classification, combines these two disorders into a single AUD with subclasses of severity. Unfortunately, despite the fact that the definition of alcohol-related disorders has been described in the DSM-V classification, the old classification is still used in Italy, defining subjects with AUD as either harmful drinkers, alcohol abusers or having alcohol dependence. This is due to delays in adopting the new classification, especially among clinicians at the local hospital level.

According to the US National Institute of Health, drinking that becomes severe is given the medical diagnosis of AUD, a chronic, relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using. AUD frequently has a progressive nature, starting with the normal consumption of alcohol, progressing to harmful or hazardous drinking, and at a later stage potentially evolving in AUD. AUD is considered a multifactorial disease, in which both environmental and genetic factors are involved in a complex way9. To be diagnosed with AUD, individuals must meet certain criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM). AUD is a risk factor for alcohol-related liver diseases (ALD) and in particular for cirrhosis, but it is still unclear whether there is a continuous dose-response relationship or a consumption threshold where the risk begins¹⁰. ALD diagnosis is mainly determined on the basis

of results and documentation relating to the consumption of alcohol of over 30 g/day for men and over 20 g/day for women and in presence of clinical and/or biological anomalies that may suggest a liver injury¹¹. Most patients suffering from ALD have been identified as asymptomatic and thus it is difficult to diagnose, but the European guidelines recommend carrying out screening with appropriate methods to identify both patients with ALD and those considered at risk¹².

A study¹³ carried out in 2012 in Spain, showed the presence of a delay between the diagnosis of ALD and the referral to a specialized alcohol unit with a median time of 40 months. This situation is also observed in daily clinical practice in the Italian setting where only a small percentage of patients are screened about their drinking habits and only one third of General Practitioners (GPs) are aware of the full or short Alcohol Use Disorder Identification Test (AUDIT) and familiar with brief interventions.

The lag-time between the occurrence of AUD and the first clinical detection may take years in daily practice, leading to a significant delay in the beginning of an intervention and potentially causing the undertreatment of this population. In Italy, there are about 700,000 people surpassing the harmful use of alcohol threshold¹⁴ – defined as consuming at least 60 g of pure alcohol per day for men and at least 40 g for women¹⁵ – but only 71,219 alcohol-dependents subjects (almost 10%) are identified and included in the National Health System (NHS) specific programs. Of these, only 28.1% are pharmacologically treated, with an overall cost of 8.2 million euros for pharmaceutical treatment¹⁶. The large discrepancy has been previously recognized at the European level¹⁷, as well as in formal national reporting¹⁴.

Morbidity and Mortality

Alcohol drinking has a relevant impact on mortality in Italy; the number of deaths for people aged 15 and over, who were registered in Italy for full alcohol-attributable diseases in 2014, was equal to 1,240, of which 224 (18.0%) were women and 1,016 (81.9%) were men. According to ISS estimates⁴, the total number of full and partial alcohol-attributable deaths is approximately 17,000 individuals each year. This corresponds to about 38 deaths per million inhabitants among men and almost 1 death per million among women. The standardized mortality rate in 2015 related to diseases totally due to alcohol consumption for the 15 years and over population was 4.06 per 100,000 inhabitants for men and 0.78 for women.

The full alcohol-attributable mortality was higher in the over 55-year population where the standardized mortality rate is 7.59 per 100,000 inhabitants among men and 1.32 per 100,000 among women, with a huge variation across Italian regions¹. In 2017, 4,575 traffic accidents were verified by local authorities or police agents as caused by alcohol. The victims involved in road accidents related to driving while drunk in 2017 were 57 (4.3% out of the total) and the injured were 4,903 (9.6% of the total). These percentages were, respectively, 5.2% and 9.2% in 2015¹⁶.

The data reported by the Ministry of Health also showed there were 39,182 requests (M: 70%, F: 30%) for emergency services caused by a major or secondary diagnosis attributable to alcohol, of which 63.8% were green code, 20.2% were yellow code, 13.5% were white code and 2.5% were red code. Of these 14.5% were due to a primary diagnosis of unspecified alcohol abuse, 14.3% to episodic alcohol abuse, and 12.8% to the toxic effects of ethyl alcohol¹⁶.

Data from the Hospital Discharge Sheets (Schede di Dimissione Ospedaliera – SDO) show the presence of 56,773 hospital discharges in 2016, following an admission due to at least one pathology attributable to alcohol, or alcohol as a major or secondary discharge diagnosis, which coexist at the time of admission and influence the therapeutic treatment administered.

Table II. The diagnosis delay and the undertreatment problem in Italy.

Difference between the number of people with a harmful level of alcohol use and people identified and included in NHS structures specific programs in Italy (2017) Delay between diagnosis of ALD and referral to a specialized treatment unit # of people with harmful use of alcohol (men >60 g/day, women >40 g/day) # of alcohol-dependents subjects that are identified and included in NHS specific programs % alcohol-dependents included in NHS programs that are pharmacologically treated Cost for pharmaceutical treatment Nedian time of 40 months 700,000 71,219 8,237,167 €

The Ministry of Health monitoring system refers to the 2007 International Classification of Diseases (ICD-9-CM) to report alcohol-related diagnoses. The diagnoses totally attributable to the use of alcohol are the following: alcohol-induced mental disorders, alcohol dependence syndromes, alcohol abuse, alcoholic polyneuropathy, cardiomyopathies, alcoholic gastritis, chronic liver disease, cirrhosis, and poisoning due to others and unspecified drugs, and toxic effects of alcohol.

In the discharge data, there is a clear prevalence of chronic hepatic diseases, such as steatosis, hepatitis, and cirrhosis (56.4% of discharges), followed by alcohol dependence syndromes, such as acute intoxication and chronic alcoholism and dipsomania (23.4%). To a lesser extent, there are the admissions due to effects posthumous to excessive casual intake of alcohol, such as hangover and intoxication (14.2%). 94.3% of the admissions were made in ordinary admission, while 5.7% were carried out during the day to perform diagnostic tests and therapies. 67.6% of the admissions diagnosed with alcohol result were urgent, while 27.3% were planned. 1% of admissions (557 admissions) were made through the Compulsory Health Treatment programme¹⁶.

The morbidity and hospitalization data show how AUD can affect a significant portion of the population, which subsequently requires a higher degree of assistance compared to primary care due to acute alcoholic hepatitis or to chronic liver disease (steatosis, steatohepatitis, fibrosis, and cirrhosis). The severity of ALD depends on the alcohol consumption (specifically the amount, pattern, and duration), as well as the presence of genetic predisposition, nutritional status, diet, and liver inflammation. Unfortunately, the incidence of the evolution to ALD is not known, and the European Guidelines indicate that progressive

liver lesions, including alcoholic hepatitis and liver fibrosis, develop and reach the cirrhosis stage for 10-35% of chronic excessive drinkers¹², but this does not result in the premature death that is much more frequent among those with alcohol dependence. Less than 10% of people with AUD in the EU receive any form of treatment for their alcohol dependence, meaning that the overwhelming majority of people with AUD receive no intervention. Treatment systems differ across Europe; but in almost all countries, the combination between psychosocial intervention and drug therapy is the backbone of treatment aimed at preventing relapses of heavy drinking^{8,18}. In Italy, the evidence is similar and represents a neglected prevention opportunity and an unmet need for inequalities in health to be tackled by the provision of available treatment. There are treatment interventions in the form of psychotherapies and pharmacotherapies that could reduce the burden of alcohol-attributable mortality. Available models estimate that a 40% rise in treatment coverage of people with AUD would reduce the death rate by some 13% in men (more than 10,000 deaths avoided at the EU level), and by some 9% in women (more than 1,700 deaths avoided at the EU level). This improvement could potentially be accomplished within 12 months. Considering this possible scenario, potentially there are significant benefits with adopting an increased level of alcohol use screening and brief interventions in primary health care for the general population. with any early detection of harmful or hazardous use integrated with the provision of treatment for harmful consumers and alcohol dependents. Benefits could include a reduction of ALD patients. as well as in the fewer instances of liver damage, progressing to the more severe stages of liver failure that often induce the onset of several forms

Table III. The distribution of hospital discharges due to diagnoses totally attributable to alcohol (*) - Year 201616.

Diagnosis at discharge	ICD-9-CM codes	Patients (%)
Alcohol-induced mental disorders	291	2,205 (3.9%)
Alcohol dependence syndrome	303	13,290 (23.4%)
Alcohol abuse	305.0	8,043 (14.2%)
Alcoholic polyneuropathy	357.5	519 (0.9%)
Alcoholic cardiomyopathy	425.5	222 (0.4%)
Alcoholic gastritis	535.30-535.31	159 (0.3%)
Chronic liver disease and cirrhosis	571.0-571.3	32,034 (56.4%)
Toxic effects of alcohol	980	5 (0.0%)
Poisoning by alcohol deterrents	977.3	296 (0.5%)
Total		56,773 (100 %)

^{*}All hospital discharges were considered as having at least one main or secondary diagnosis totally attributable to alcohol.

of complications, such as hepatic encephalopathy (HE), hepatocellular carcinoma (HCC) or liver transplantation^{19,20}. HE is a serious neuropsychiatric complication of cirrhosis in alcoholic patients that is characterized clinically by personality changes, sleep abnormalities, and impaired motor coordination, as well as cognitive dysfunction progressing to stupor and coma²¹. In patients with HE, the damaged liver can no longer remove neurotoxic substances, such as ammonia and manganese from the blood, and thus they enter the brain and interfere with normal neurotransmitter activity, impair motor functions, and cause structural alterations in the astrocytes²².

ALD can also evolve into fatty liver disease, cirrhosis, and hepatocellular carcinoma. Patients with alcohol cirrhosis have a greater risk of liver decompensation than patients with cirrhosis due to other causes. Burra et al²³ highlight that "nowadays, in Europe, alcohol excessive consumption accounts for 40-50% of all liver cancer cases and, with the sharp decline of chronic viral hepatitis, it has been estimated that alcohol will become the leading cause of liver cancer, at least in developed countries"²³. In Italy, there are 33,000 people with a previous diagnosis of HCC and, in 2018, 12,800 new cases of HCC were estimated²⁴. A research²⁵ in Italy and in the USA has shown that alcohol is responsible for an estimated 32% to 45% of HCC cases.

ALD can also lead to liver transplantation. Alcohol appears to be the sole cause of liver transplantation in 33% of cases, while the percentage rises to 37% when ALD is a comorbidity to hepatitis B/C²⁶.

Alcohol use is associated with worse prognosis in HCV-related liver disease, with an estimated 36% of liver cirrhosis cases among HCV-infected individuals attributable to alcohol use²⁷. The relationship between HCV and alcohol consumption is well known. Alcohol consumption is responsible for the 70-90% of all liver disease cases from chronic hepatitis C viral infection in Western countries. Furthermore, 80% of deaths due to liver disease are attributed to alcohol, as well as 44% of deaths due to cirrhosis²⁸. Due to the increase in the availability of new treatments aimed at eradicating hepatitis caused by virus, in the future, cirrhosis and liver cancer likely will be linked mainly to harmful use of alcohol.

Critical Issues and Possible Interventions

The issues presented in this paper show that AUD represents a growing concern for public health and an appropriate national action plan is urgently required to encourage patients to turn to

specialized alcohol units at the initial stage of the disease and before the need of liver transplantation²⁸. A popular strategy supported by the results of several meta-analyses is the approach defined by the acronym SBIRT: Screening, Brief Intervention, and Referral to Treatment²⁹, which consists of a public health framework approach that is used to identify and deliver services to those at risk for substance-use disorders, depression, and other mental health conditions.

Several guidelines recommend its implementation at the global level, particularly in primary care³⁰. There are many tools to perform the initial screening³¹, but the gold standard is considered the AUDIT instrument, of which two versions have been developed. The full AUDIT-10 has shown criteria sensitivity and specificity of 92% and 94% respectively and consists of 10 questions that explore 3 fields: consumption, addiction, and alcohol-related problems.

Even though the shorter version called AU-DIT-C includes only the first three questions of the AUDIT and is reliable only for the screening of 'risky drinking', it has shown high sensitivity and a specificity of 86% and 72% respectively¹².

A problem observed by specialists in this field is the difficulty of GPs to perform accurate and widespread screening, and often they tend to minimize the problem by giving little value to patients' responses and accepting superficial responses³². In particular, the ability and knowledge of GPs to identify people with AUD appears lacking, as a systematic review has shown that the diagnostic sensitivity of GPs in identifying AUD appears to be 41.7% (95% CI 23.0-61.7), but the alcohol problems were correctly recorded only in 27.3% (95% CI 16.9-39.1). These data were obtained from studies in Germany and the United States, and similar data in the Italian setting would be of value³³.

In a more recent study concerning access to primary care in 6 EU countries including Italy, showed that about 9% of patients coming from GPs suffered from AUD, but it was recognised in only 5% of these patients and only 20% of these received treatment. This problem is also called "double interruption of treatment"³⁴.

Unfortunately, although the guidelines give clear indications on interventions and treatments for people with AUD, their implementation in clinical practice is still difficult⁸. A common recommendation is the implementation of autonomous management between GPs through counselling since it has been observed to be effective and as there is still no uniformity of action between

GPs³². Referral for treatment to a specialist doctor is recommended only for patients who show signs of ALD¹².

A European program, called BISTAIRS (Brief interventions in the treatment of alcohol use disorders in relevant settings), aims to intensify the implementation of brief counselling sessions for risky drinkers in primary health care facilities, places of work, and social services. This would allow the uniform management of patients with AUD by providing guidelines to doctors for use in their clinical practice³⁵. The recent WHO European Alcohol Action Plan to Reduce the Harmful Use of Alcohol³⁶ recommends screening and brief intervention programs as a key strategy for health services throughout the continent and the use of SBIs (Screening and Brief Interventions) in primary care are currently recommended in Italian national guidelines³⁷. Indeed, providing interventions to the AUD population at an early stage could prevent the onset of liver problems³⁵. Furthermore, a study was conducted to evaluate a program of screening and brief interventions in Italy by adapting the Sheffield Alcohol Policy Model, a model used to estimate the cost-effectiveness of government pricing and public health policies. The model results showed that SBI programs are highly cost-effective, with an estimated ICER (Incremental Cost-Effectiveness Ratio) of €550/ Quality Adjusted Life Year (QALY) gained for a program of SBIs at the next GP registration and €590/OALY for SBI at the next GP consultation³⁸. Thus, the study supported instituting a policy of screening and brief interventions throughout Italy. To confirm the potential of the BISTAIRS approach, a meta-analysis was published by the AMPHORA project that supported implementing short interventions in a primary care setting. On the other hand, the AMPHORA project also reported some critical issues that can arise when these interventions have to be applied in the clinical practice, including the difficulties of many clinicians to guarantee this type of service³⁹ and the difficulty detecting AUD in many people. The so-called therapeutic gap, representing the difference between people who are able to access this type of treatment or program and the number of people with AUD, highlights the importance of implementing the BISTAIRS program⁴⁰. Italy appears to be the country with the highest access (23.3%) to the BISTAIRS program compared with six other European countries, while England is the country with the smallest percentage of access (7.1%) in the countries reviewed⁴⁰. However,

there are still some barriers to implement these screening and short intervention programs (when necessary):

- time limitations (though the recommended time for a brief intervention is 5-10 minutes per patient);
- lack of training (though 54% of GPs surveyed reported receiving 4 or more hours of education and training on the management of alcohol problems)⁴¹;
- lack of simple materials to use;
- lack of specialist services to target patients with more severe alcohol consumption problems.

Therefore, there are still gaps to be filled in order to implement the most recent strategies proposed by the BISTAIRS program. For example, it has been observed across European countries that primary care providers have not managed to improve their approach to the provision of interventions, which remained almost the same during the last 10-20 years.

Given this issue, the WHO recommends that governments support the SBI programs and ensure that clinical guidelines for such interventions are available; they should also provide training, materials, and clinical tools to GPs in order to establish these programs, together with adequate economic resources⁴⁰.

Therefore, it is essential to ensure that there are adequate interventions and evidence-based practices for people with alcohol dependence and potential liver damage. These can include training for all healthcare professionals at the primary health care level (e.g., GPs, sports doctors), caregiver and family training, information campaigns to facilitate a proper diagnosis, the integration of an early identification and brief intervention program (such as BISTAIRS), the integration of standard screening formats through questionnaires (such as AUDIT) for detecting harmful and hazardous drinking, the creation of innovative intervention protocols and integrated networks between GPs, hospitals and other healthcare providers, and facilitating communication with selfhelp groups that aim to facilitate recovery from AUD and lower the risk of relapse. A primary goal could be to increase the level of treatment for AUD in order to reduce the higher mortality risk that is a result of missed opportunities to detect the problem early. Addressing this issue could lead to a higher level of inclusion in a rehabilitative program for the majority of harmful drinkers currently representing a neglected target of prevention.

Conclusions

Alcohol risk prevention is a neglected target in public health policy. When considering the treatment of alcohol related diseases, the gap between harmful drinkers and people with AUD eligible for treatment and those in any form of treatment represents an example of inequalities in health. Furthermore, there is considerable variation in the implementation of alcohol interventions and treatment for individuals at a higher risk of comorbidity and mortality that could be partially lowered by an appropriate program of medical screening and therapies.

There is a need for a more concerted effort to consider the training of primary care health professionals to enable renewed networks for the early identification of hazardous drinkers to prevent the occurrence of avoidable alcohol related conditions and ALD, while implementing, as soon as possible, evidence-based brief interventions. A universal, general population prevention approach needs to be integrated and combined with offering adequate forms of treatment to AUD individuals by enabling and strengthening access to rehabilitation programs.

Strengthening monitoring systems aimed at improving the estimation of the prevalence of AUD, monitoring the implementation of an early identification system and treatment, and the evaluation of the effectiveness of treatment are also needed. These will capture the improvement of the quality of life and health status for harmful and hazardous drinkers who have been empowered to control their drinking and improve their own health and wellness through a new program of screening and interventions.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

- 1) Istituto Superiore di Sanità. Epidemiologia e monitoraggio alcol-correlato in Italia e nelle Regioni. Valutazione dell'Osservatorio Nazionale Alcol sull'impatto del consumo di alcol ai fini dell'implementazione delle attività del Piano Nazionale Alcol e Salute. Rapporto 2018. Rapporto Istisan.
- MONTONEN M, MÄKELÄ P, SCAFATO E, GANDIN C ON BEHALF OF JOINT ACTION RARHA. Good practice principles for low risk drinking guidelines. 2016. http:// www.julkari.fi/handle/10024/131322.

- ENDORSED BY THE COMMITTEE ON NATIONAL ALCOHOL POLICY AND ACTION (CNAPA). Action Plan on Youth Drinking and on Heavy Episodic Drinking (Binge Drinking), 2014. https://ec.europa.eu/health//sites/health/files/alcohol/docs/2014_2016_actionplan_youthdrinking_en.pdf
- 4) ADDOLORATO G, VASSALLO GA, ANTONELLI G, ANTONELLI M, TARLI C, MIRIJELLO A, AGYEI-NKANSAH A, MENTELLA MC, FERRARESE D, MORA V, BARBÀRA M, MAIDA M, CAMMÀ C, GASBARRINI A; Alcohol Related Disease Consortium. Binge drinking among adolescents is related to the development of Alcohol Use Disorders: results from a cross-sectional study. Sci Rep 2018; 8: 12624.
- SCAFATO E, GANDIN C, DI PASQUALE L, GALLUZZO L, MARTIRE S, GHIRINI S. Epidemiologia e monitoraggio alcol-correlato in Italia e nelle regioni. Rapporto 2016. Rapporti Istisan Epidemiologia e Sanità Pubblica, 2016; Vol. 16/4.
- REHM J, SCAFATO E. Indicators of alcohol consumption and attributable harm for monitoring and surveillance in European Union countries. Addiction 2011; 106: 4-10.
- 7) SISTEMA ITALIANO MONITORAGGIO ALCOL. Sistema Italiano Monitoraggio Alcol. https://www.epicentro.iss. it/alcol/SismaMonitoraggio.
- ADDOLORATO G, MIRUELLO A, BARRIO P, GUAL A. Treatment of alcohol use disorders in patients with alcoholic liver disease. J Hepatol 2016; 65: 618-630
- PALMER RH, McGEARY JE, HEATH AC, KELLER MC, BRICK LA, KNOPIK VS. Shared additive genetic influences on DSM-IV criteria for alcohol dependence in subjects of European ancestry. Addiction 2015; 110: 1922-1931.
- REHM J, TAYLOR B, MOHAPATRA S, IRVING H, BALIUNAS D, PATRA J, ROERECKE M. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev 2010; 29: 437-445.
- 11) Askgaard G, Leon DA, Kjaer MS, Deleuran T, Gerds TA, Tolstrup JS. Risk for alcoholic liver cirrhosis after an initial hospital contact with alcohol problems: a nationwide prospective cohort study. Hepatology 2017; 65: 929-937.
- 12) EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER. EASL Clinical Practice Guidelines: management of alcohol-related liver disease. J Hepatol 2018; 69: 154-181.
- 13) ALTAMIRANO J, BATALLER R, CARDENAS A, MICHELENA J, FREIXA N, MONRÁS M, RÍOS J, LICCIONI A, CABALLERÍA J, GUAL A, LLIGOÑA A. Predictive factors of abstinence in patients undergoing liver transplantation for alcoholic liver disease. Ann Hepatol 2012; 11: 213-221.
- 14) ISTITUTO SUPERIORE DI SANITÀ, ORGANIZZAZIONE MONDIALE DELLA SANITÀ. Confermato l'aumento dei consumi di alcol in Italia. 2017.
- 15) REHM J, SHIELD KD, REHM MX, GMEL G, FRICK U. Alcohol consumption, alcohol dependence, and attributable burden of disease in Europe: potential gains from effective interventions for alcohol dependence 2012; 8: 21.

- 16) MINISTERO DELLA SALUTE. Relazione del ministro della salute al parlamento sugli interventi realizzati ai sensi della legge 30.3.2001 n. 125 "legge quadro in materia di alcol e problemi alcol correlati". 2017.
- 17) DRUMMOND C, GUAL A, GOOS C, GODFREY C, DELUCA P, VON DER GOLTZ C, GMEL G, SCAFATO E, WOLSTENHOLME A, MANN K, COULTON S, KANER E. Identifying the gap between need and intervention for alcohol use disorders in Europe. Addiction 2011; 106: 30-35.
- 18) CAPUTO F, VIGNOLI T, GRIGNASCHI A, CIBIN M, ADDO-LORATO G, BERNARDI M. Pharmacological management of alcohol dependence: From mono-therapy to pharamcogenetics and beyond. Eur Neuropsychopharmacol 2014; 24: 181-191.
- MATHURIN P, BATALLER R. Trends in the management and burden of alcoholic liver disease. J Hepatol 2015; 62: S38-S46.
- BRUHA R, DVORAK K, PETRTYL J. Alcoholic liver disease. World J Hepatol 2012; 27; 4: 81-90.
- 21) BUTTERWORTH RF. Hepatic encephalopathy in alcoholic cirrhosis. Handb Clin Neurol 2014; 125: 589-602.
- BUTTERWORTH RF. Hepatic encephalopathy—a serious complication of alcoholic liver disease. Alcohol Res Health 2003; 2: 143-145.
- 23) Burra P, Zanetto A, Germani G. Liver transplantation for alcoholic liver disease and hepatocellular carcinoma. Cancers (Basel) 2018; 10: 46.
- 24) AIOM. Linee Guida epatocarcinoma. 2018.
- 25) Testino G, Leone S, Borro P. Alcohol and hepatocellular carcinoma: a review and a point of view. World J Gastroenterol 2014; 20: 15943-15954.
- VARMA V, WEBB K, MIRZA DF. Liver transplantation for alcoholic liver disease. World J Gastroenterol 2010; 16: 4377-4393.
- 27) FUSTER D, SANVISENS A, BOLAO F, RIVAS I, TOR J, MUGA R. Alcohol use disorder and its impact on chronic hepatitis C virus and human immunodeficiency virus infections. World J Hepatol 2016; 8: 1295-1308.
- 28) Testino G, Burra P, Bonino F, Piani F, Sumberaz A, Peressutti R, Giannelli Castiglione A, Patussi V, Fanucchi T, Ancarani O, De Cerce G, Iannini AT, Greco G, Mosti A, Durante M, Babocci P, Quartini M, Mioni D, Aricò S, Baselice A, Leone S, Lozer F, Scafato E, Borro P. Acute alcoholic hepatitis, end stage alcoholic liver desease and liver transplantation: an Italian position statement. World J Gastroenterol 2014; 10: 14642-14651.
- 29) O'Donnell A, Anderson P, Newbury-Birch D, Schulte B, Schmidt C, Reimer J, Kaner E. The impact of brief alcohol interventions in primary healthcare: a systematic review of reviews. Alcohol Alcohol 2014; 49: 66-78.
- 30) Jonas DE, Garbutt JC, Amick HR, Brown JM, Brown-LEY KA, Council CL, Viera AJ, Wilkins TM, Schwartz CJ, Richmond EM, Yearts J, Evans TS, Wood SD, Harris RP. Behavioral counseling after screening for alcohol misuse in primary care: a systematic

- review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2012; 157: 645-654.
- 31) FEDERICO A, COTTICELLI G, FESTI D, SCHIUMERINI R, ADDOLORATO G, FERRULLI A, MERLI M, LUCIDI C, MILANI S, PANELLA C, DOMENICO M, VANTINI I, BENINI L, UBALDI E, ROMANO M, LOGUERCIO C. The effects of alcohol on gastrointestinal tract, liver and pancreas: evidence-based suggestions for clinical management. Review. Eur Rev Med Pharmacol Sci 2015; 19: 1922-1940.
- 32) REHM J, ANDERSON P, MANTHEY J, SHIELD KD, STRUZZO P, WOJNAR M, GUAL A. Alcohol use disorders in primary health care: what do we know and where do we go? Alcohol Alcoholism 2016; 51: 422-427.
- 33) MITCHELL AJ, MEADER N, BIRD V, RIZZO M. Clinical recognition and recording of alcohol disorders by clinicians in primary and secondary care: meta-analysis. Br J Psychiatry 2012; 201: 93-100.
- 34) REHM J, ALLAMANI A, DELLA VEDOVA R, ELEKES Z, JAKUBCZYK A, LANDSMANE I, MANTHEY J, MORENO-ESPAÑA J, PIEPER L, PROBST C, SNIKERE S, STRUZZO P, VOLLER F, WITTCHEN HU, GUAL A, WOJNAR M. General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 European countries. Ann Fam Med 2015; 13: 28-32.
- 35) Anderson P, O'Donnell A, McCormick R. Managing risky drinking in primary care settings. Good practice guidance to identify, assess and manage risky drinking in primary health care, emergency care, workplace and social service settings. 2013; Version 1.3, Vol. September.
- 36) WORLD HEALTH ORGANIZATION. European Action Plan to Reduce the Harmful use of Alcohol 2012-2020. Copenhagen, Denmark: World Health Organisation Regional Office for Europe, 2012.
- MINISTERO DELLA SALUTE. Piano Nazionale Alcol e Salute, 2007.
- 38) ANGUS C, SCAFATO E, GHIRINI S, TORBICA A, FERRE F, STRUZZO P, PURSHOUSE R, BRENNAN A. Cost-effectiveness of a programme of screening and brief interventions for alcohol in primary care in Italy. BMC Fam Pract 2014; 15: 26.
- 39) ELZERBI C, DONOGHUE K, DRUMMOND C. The public health impact of individually directed brief interventions and treatment for alcohol use disorders in European countries and worldwide. Report prepared for the AMPHORA project. www.amphoraproject. 2013.
- COLOM J, SCAFATO E, SEGURA L, GANDIN C, STRUZZO P. Brief interventions implementation on alcohol from the European health systems perspective front psychiatry. Front Psychiatry 2014; 5: 161.
- 41) Wojnar M, Jakubczyk A, Anderson P, Gaby R, Kaner E, Kolsek M, Laurant M, Newbury-Birch D, Ribeiro C, Segura L, Sovinova H, Spak F, Struzzo P, Gual A. Attitudes and managing alcohol problems in general practice in Europe: results from the European ODHIN study. Alcohol Alcoholism 2014; 5: 531-539.