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An interrupted time series analysis of hospital admissions due to alcohol intoxication during the COVID-19 pandemic in Tehran, Iran

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The COVID-19 outbreak affected mental health globally. One of the major concerns following the COVID-19 pandemic was increased incidence of risky behaviors including alcohol consumption. This study evaluates the trend of alcohol poisoning in Loghman-Hakim Hospital (LHH), the main referral center of poisoning in Tehran, during the 2-year period from 1 year prior to 1 year after the onset (February 23rd, 2020) of the COVID-19 epidemic in Iran. All patients admitted with alcohol intoxication from February 23rd, 2019 to February 22nd, 2021 were evaluated and patient data extracted from LHH electronic hospital records. Alcohols were categorized as toxic (methyl alcohol) and non-toxic (ethyl alcohol). Of 2483 patients admitted, 796/14,493 (5.49%) and 1687/13,883 (12.15%) had been hospitalized before and after the onset of the COVID-19 epidemic in Iran, respectively. In total, 140 patients did not survive, of whom 131 (93.6%) were confirmed to have methanol intoxication. Mortality was significantly higher during the outbreak (127 vs 13; $P < 0.001$; OR: 4.90; CI 95%: 2.75 to 8.73). Among the patients, 503 were younger than age 20. Trend of alcohol intoxication showed increases in children (57 vs 17) and adolescents (246 vs 183) when compared before and after the COVID-19 epidemic outbreak. A total of 955 patients were diagnosed with methanol toxicity which occurred more frequently during the COVID-19 era (877 vs 78; $P < 0.001$; OR: 10.00; CI 95%: 7.75 to 12.82). Interrupted time series analysis (April 2016–February 2021) showed that in the first month of the COVID-19 epidemic (March 2020), there was a significant increase in the alcohol intoxication rate by 13.76% ($P < 0.02$, CI = [2.42–24.91]). The trend of alcohol intoxication as well as resulting mortality increased in all age groups during the COVID-19 epidemic in Iran, indicating urgent need for the prevention of high-risk alcohol use as well as improved treatment.

Abbreviations

CI	Confidence Interval
GCS	Glasgow Coma Scale
HD	Hemodialysis
OR	Odds Ratio
SPSS	Statistical Package for the Social Sciences
VDs	Visual disturbances
WHO	World Health Organization

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The COVID-19 pandemic influenced people's mental health globally¹. Anxiety, panic, post-traumatic stress disorder (PTSD), and depression were among the numerous detrimental effects of this pandemic on people's minds². The implemented strategies to control the infection have been based primarily on physical and social isolation like the closure of universities, schools and social events, mandatory facial mask use, ban of international travels and remote working^{3,4}. These restrictive measures are shown to be related to the incidence of anxiety, depression, PTSD, sleep disorders, lack of self-control, and impaired self-esteem⁵. Media coverage of pandemic news has been another stressor to cause anxiety and fear in the population⁶. In addition, infected individuals have been exposed to an even higher incidence of mental disorders including depression, anxiety, and PTSD⁷. A cohort analysis revealed that almost one in five COVID 19 survivors was diagnosed with a psychiatric condition in 3 months after the infection⁸. A meta-analysis found that almost one-third of COVID 19 survivors experienced anxiety and depressive symptoms⁹. The mental consequences of the pandemic have been even more detrimental for the individuals with background mental disorders leading to the exacerbation of their conditions¹⁰. One of the consequences was increased risky behaviors including alcohol consumption and substance use¹¹.

Alcohol use is believed to be the seventh leading risk factor for disability and premature death, and it is estimated that almost one-third of the global population drinks alcohol¹². Alcohol consumption has been linked with vehicle accidents and related fatalities, domestic violence, suicide, and child abuse, all of which were therefore expected to occur more frequently during the COVID-19 pandemic^{13,14}. Studies on the general population have found a connection between common mental disorders like anxiety and depression with binge drinking and alcohol use disorder^{15–18}. In a study among college students, individuals with anxiety and depressive symptoms expressed a higher rate of weekly alcohol usage, and more adverse outcomes in comparison to individuals without symptoms¹⁹. In another study, anxiety and depression have been associated with 1.5 times more probability to alcohol abuse and 2.5 times to alcohol dependence¹⁸. A similar study found the same results in addition to the finding of PTSD to be related to two times higher probability of alcohol use disorder incidence²⁰. Also, there is evidence of the association between increasing alcohol use and the worsening of mental health²¹. Coping with the stress is argued as a reason for alcohol consumption by motivational models as a mean for alleviation of the mental disorder symptoms^{22,23}.

Reports show an increase in the trend of alcohol consumption throughout the world during the pandemic²⁴. In Iran, there is no national center to monitor this trend. Additionally, alcohol consumption is prohibited in this country making the black market as the main source of provision of alcoholic beverages to the society and tracking a record on alcohol sale and use even more difficult. Along with criminalization due to the ban on alcohol in Iran, stigma is another factor that prevents individuals from seeking help and finding proper treatment; exposing them to more deleterious outcomes²⁵.

This study evaluates the trend of alcohol intoxication (both toxic and non-toxic alcohols) in patients admitted to Lohman-Hakim Hospital (LHH), the main referral center for poisoned patients in the capital city of Tehran in the year preceding the COVID-19 outbreak and the year following its announcement in three different age groups of children, adolescents, and adults.

Materials and methods

Setting and study design. In a retrospective cross-sectional study, all alcohol-intoxicated patients admitted to LHH from February 23rd, 2019 to February 22nd, 2021 were enrolled into the study. February 23rd, 2020 was the date of announcement of COVID-19 epidemic in Iran (declared by the Iranian ministry of health) and was considered as the official date of COVID-19 initiation. LHH has the highest in-patient clinical toxicology admissions (25,000 patients/year) worldwide²⁶.

Age categorization. Patients aged 12 and younger were considered as children. The adolescent group consisted of the patients 13–20 years of age and all those 21 years and older were considered as adults.

Type of alcohol. All patients with serum methanol level >6.25 mmol/L (20 mg/dL) were considered as methanol-intoxicated (either solely or in a co-ingestion with other medications/drugs/substances)²⁷. Patients with an ethanol level higher than 50 mg/dL were considered as ethanol-poisoned again either solely or in combination with other medications/drugs/substances²⁸.

Epidemiological data and COVID-19 categorization. Patients' demographic characteristics (age, gender), final diagnosis, and their final outcome were retrieved from the LHH electronic archive and analyzed.

Missing data and statistical analysis. Data was analyzed using statistical package for social sciences (SPSS) software version 26 (IBM CO., Chicago, Ill, USA). Comparing parts with missing and non-missing data, it appears that missing data was completely random and randomly distributed across all observations. Chi-Square and Fisher's exact tests were applied to search for significant differences in the categorical variables. The 95% confidence interval (CI) was used to estimate the precision of the odds ratio (OR). Mann-Whitney test applied to see differences among age and expressed as median [Inter quartile range]. Stata 14.0 (Stata Corp LLC, College Station, Texas, USA) was used for interrupted time series analysis to see whether the COVID-19 pandemic resulted in a shift in the level and trend of alcohol intoxication compared with those of the pre-COVID-19 period. We set the significance level at alpha = 0.05. For specific aim of time series analysis, data on the trend of alcohol intoxication was also gathered from April 2016 till February 2019 for a better assessment of pre-pandemic trend.

Age group	Gender		Methanol n (%)	Ethanol n (%)	Co-ingestion n (%)	P1 (M ¹ vs. E ²)	P2 (M vs. C ³)	P3 (C vs.E)
Children (n = 74)	Female (n = 27)	Pre COVID (n = 6)	0	5 (83.7)	1 (16.7)	0.278 [‡]	0.125 [‡]	0.300 [‡]
		During COVID (n = 21)	7 (33.3)	14 (66.7)	0			
	Male (n = 47)	Pre COVID (n = 11)	1 (9.1)	10 (90.9)	0	0.078 [‡]	–	–
		During COVID (n = 36)	14 (38.9)	22 (66.1)	0			
	Both (n = 74)	Pre COVID (n = 17)	1 (5.9)	15 (88.2)	1 (5.9)	0.028 [‡] 8.77* [1.08, 71.43]	0.087 [‡]	0.308
		During COVID (n = 57)	21 (36.8)	36 (63.2)	0			
Adolescents 13–20 (n = 429)	Female (n = 87)	Pre COVID (n = 33)	2 (6.1)	15 (45.5)	16 (48.5)	0.007 [‡] 7.94* [1.58, 7.94]	0.003 [‡] 8.93* [6.29, 45.45]	0.805
		During COVID (n = 54)	19 (35.8)	17 (32.1)	17 (32.1)			
	Male (n = 342)	Pre COVID (n = 150)	10 (6.7)	78 (52)	62 (41.3)	< 0.001 4.38* [2.29, 10.53]	< 0.001 5.43* [0.071, 0.374]	0.468
		During COVID (n = 192)	52 (27.1)	84 (43.8)	56 (29.2)			
	Both (n = 429)	Pre COVID (n = 183)	12 (6.6)	93 (50.8)	78 (42.6)	< 0.001 5.35* [2.75, 10.52]	< 0.001 5.43* [2.67, 12.66]	0.465
		During COVID (n = 246)	71 (29.2)	101 (41.2)	73 (29.8)			
Adults > 20 (n = 1980)	Female (n = 379)	Pre COVID (n = 127)	10 (7.9)	41 (32.3)	76 (59.8)	< 0.001 8.20* [3.84, 17.54]	< 0.001 14.28* [6.94, 29.41]	0.034 1.74* [1.04, 2.91]
		During COVID (n = 252)	124 (49.2)	62 (24.6)	66 (26.2)			
	Male (n = 1601)	Pre COVID (n = 469)	50 (10.7)	265 (56.5)	154 (32.8)	< 0.001 11.23* [8.06, 15.62]	< 0.001 8.85* [6.21, 12.66]	12.5
		During COVID (n = 1132)	622 (54.9)	293 (25.9)	217 (19.2)			
	Both (n = 1980)	Pre COVID	60 (10.1)	306 (51.3)	230 (38.6)	< 0.001 10.75* [8.06, 15.62]	< 0.001 10.10* [7.35, 13.89]	0.637
		During COVID	746 (53.9)	355 (25.7)	283 (20.4)			
All ages (n = 2483)	Female (n = 493)	Pre COVID (n = 166)	12 (7.2)	61 (36.7)	93 (56)	< 0.001 8.13* [4.15, 15.87]	< 0.001 14.08* [7.25, 27.03]	0.015 1.73* [1.11, 2.88]
		During COVID (n = 327)	150 (46)	93 (28.5)	83 (25.5)			
	Male (n = 1990)	Pre COVID (n = 630)	61 (9.7)	353 (56)	216 (34.3)	< 0.001 10* [7.41, 13.51]	< 0.001 8.93* [6.49, 12.19]	0.339
		During COVID (n = 1360)	688 (50.6)	399 (29.3)	273 (20.1)			
	Both (n = 2483)	Pre COVID (n = 796)	73 (9.2)	414 (52)	309 (38.8)	< 0.001 9.61* [7.35, 12.66]	< 0.001 10* [7.52, 13.15]	0.747
		During COVID (n = 1687)	838 (49.7)	493 (29.2)	356 (29.1)			

Table 1. Number of alcohol intoxications and patients' characteristics before and during COVID-19 outbreak (n = 2483). [‡]Applying Fisher's Exact test, *OR (95% CI), M¹ (Methanol), E² (Ethanol), C³ (Co-ingestion).

Ethics approval and consent to participate. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1399.149). All experiments were in accordance with Helsinki declaration. Informed consent was obtained from all participants and/or if participants are under 16, from a parent and/or legal guardian.

Results

Epidemiological data. *Age and gender.* Of the 2483 patients referred to LHH with alcohol intoxication during the study period (out of a total of 28,376 patients hospitalized with poisoning), 1990 (80.1%) were male and 493 (19.9%) were female (Table 1). The mean (SD) age was 31.58 ± 13.76 (range: 1–87) years. A total of 796 out of 14,493 (32.1% of total alcohol cases of the study period and 5.49% of pre-COVID-19 cases) and 1687 out of 13,883 (67.9% total alcohol cases of the study period and 12.15% of during COVID-19 cases) had referred before and after the COVID-19 pandemic initiation in Iran. There were 361/14,493 (2.49%) vs. 474/13,883 (3.41%) deaths in hospitalized patients pre-COVID-19 vs. during COVID-19 respectively. Alcohol-related death was more common during COVID-19 period (127 vs. 13; P < 0.001; OR: 4.90; CI 95%: 2.75–8.73). Of the 796 patients referred before the infectious epidemic, 166 (20.8%) were female and 630 (79.2%) were male whereas in the 1687 admitted during the outbreak, 327 (19.4%) were female and 1360 (80.6%) were male. No significant difference was detected between the patients regarding their gender before and during the outbreak (P was nonsignificant).

Alcohol type and mortality. In the 2-years scope of the study, 140 (5.64% of total alcohol cases and 16.77% of total mortalities due to poisoning) alcohol intoxicated patients died (21 females and 119 males). Mortality rates were 1.6% and 7.5% of alcohol intoxicated cases before and after the COVID-19 epidemic, respectively (13 versus 127 deaths; P < 0.001; OR = 4.90; CI 95% = 2.75–8.73). Figure 1 shows the trend of alcohol intoxication (Fig. 1A) and mortality (Fig. 1B) for each month in the period of the study. A total of 131 out of 140 (93.6%) non-survivors were intoxicated by methanol (solely or in combination with other medications/substances).

Of the total population of the study, 955 (38.5%) were diagnosed with methanol poisoning, either as a sole intoxicant (928; 37.4%) or with drugs/medications (27; 2.8%). Among 928 cases, 74 and 854 admitted before and after the COVID-19 epidemic respectively; P < 0.001; OR = 10.00; CI 95% = 7.73–12.94). Mortality was

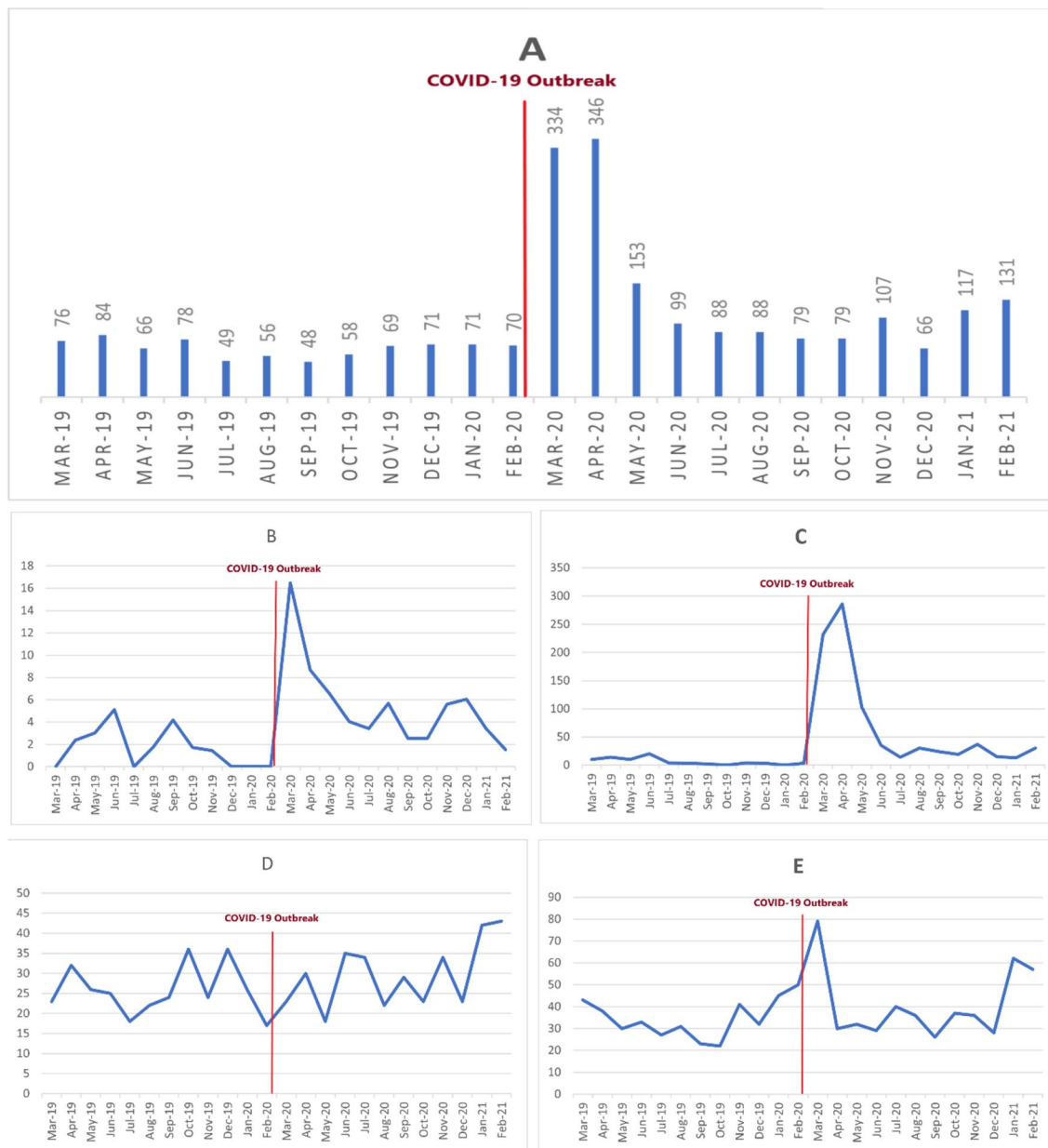


Figure 1. The trend of alcohol intoxication in the population: (A) all alcohols, (B) trend of mortality, (C) methanol, (D) co-ingestions, E ethanol.

significantly higher among methanol-poisoned patients ($P < 0.001$; OR = 6.54; CI 95% = 4.35–9.84). Of 140 deaths, 131 (93.6%) had occurred among the patients diagnosed with methanol poisoning (mortality rate = 11.75%). Of this note, 5 patients (3.6%) consumed methanol in addition to at least one substance/medication.

Almost 27% (665 patients) of our cases had been admitted with mixed poisoning of alcohols and other substances/medications, of whom 44 and 621 were finally diagnosed with methanol and ethanol intoxication as the alcohol involved in the intoxication, again with no significant difference between the pre- and during-COVID epidemic. Table 2 shows the pair comparisons of three groups together. Mortality was significantly higher before and during-COVID epidemic while methanol was compared to ethanol ($P = 0.016$; OR = 29.41; CI 95% = 2.41–333.3) or to the patients who had co-ingestion ($P = 0.045$; OR = 9.71; CI 95% = 7.25–13.18). No significant differences were found between ethanol and co-ingestion group in alive or dead cases any time. Only 11 patients with mixed poisoning did not survive (mortality rate = 1.65%). Figure 1C,D depict the trend of poisoning with methanol and mixed poisoning during the study period, respectively. Trend of alcohol intoxication among children (A), adolescents (B), and Adults (C) Pre-COVID 19 and during COVID-19 are shown in Fig. 2.

Interrupted time series analysis (April 2016–February 2021). *Alcohol intoxication.* As shown in Table 3 and Fig. 3, the alcohol intoxication rate increased every month before March 2020 by 0.04%. This increase was statistically significant ($P = 0.03$, CI = [0.01–0.07]).

	Survived (n = 2703)		Death (n = 140)	
	Pre COVID-19 (n = 783)	During COVID-19 (n = 1560)	Pre COVID-19 (n = 13)	During COVID-19 (n = 127)
Methanol n (%)	65 (2.40)	720 (26.64)	8 (5.71)	118 (84.28)
Ethanol n (%)	414 (15.3)	492 (18.20)	2 (1.43)	1 (0.71)
P-value	<0.001		0.016	
OR (95% CI)	9.26 (12.34, 6.99)		29.41 (2.41, 333.33)	
Co-ingestion n (%)	306 (11.32)	348 (12.87)	3 (2.14)	8 (5.71)
Ethanol n (%)	414 (15.31)	492 (18.20)	1 (0.71)	2 (1.43)
P-value	0.643		0.505	
OR (95% CI)	5.52 (1.22, 25.00)		9.71 (7.25, 13.18)	
Methanol n (%)	65 (2.40)	720 (26.64)	8 (5.71)	118 (84.28)
Co-ingestion n (%)	306 (11.32)	348 (12.87)	3 (2.14)	8 (5.71)
P-value	<0.001		0.045	
OR (95% CI)	5.52 (1.22, 25.00)		9.71 (7.25, 13.18)	

Table 2. Comparison of different groups of alcoholic ingestions 1 year before and after COVID-19 (n = 2483).

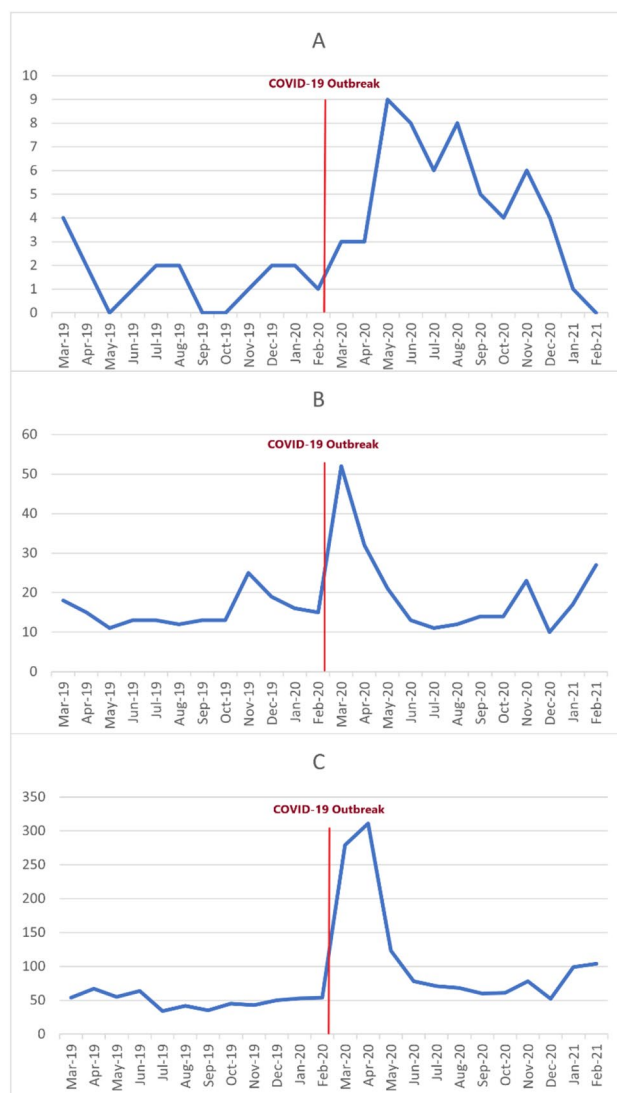


Figure 2. Trend of alcohol intoxication among children (A), adolescents (B), and Adults (C) Pre-COVID 19 and during COVID-19.

Variable	Coef	SE	P	95% CI
Alcohol intoxication				
cons	4.34	0.49	<0.001	3.35 to 5.34
_t	0.04	0.02	0.03	0.01 to 0.07
_x48	13.67	5.61	0.02	2.42 to 24.91
_x_t48	-1.44	0.73	0.05	-2.91 to 0.02
Treated	-1.41	0.73	0.06	-2.84 to 0.02
Alcohol-related mortality				
cons	1.78	0.50	0.001	0.77 to 2.79
_t	-0.01	0.02	0.47	-0.05 to 0.02
_x48	8.50	2.47	0.001	3.54 to 13.47
_x_t48	-0.73	0.31	0.02	-1.35 to -0.10
Treated	-0.74	0.31	0.02	-1.36 to -0.12

Table 3. Interrupted time series analysis comparing level, trend and mortality of alcohol intoxication in pre-COVID-19 to during COVID-19 period.

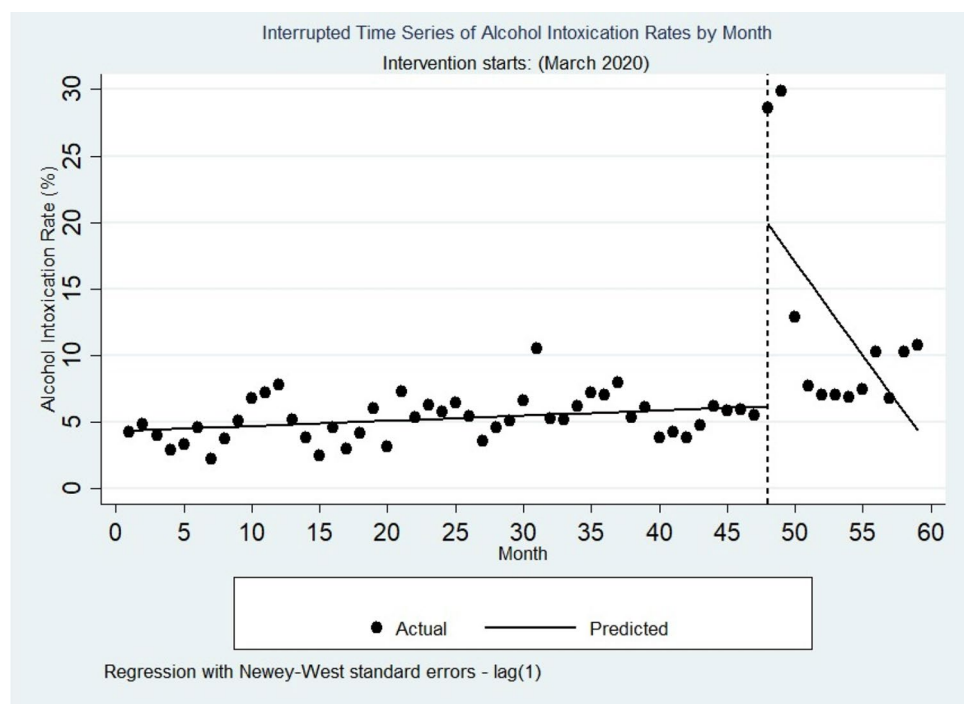


Figure 3. Interrupted time series of alcohol intoxication rates by month.

In the first month of the COVID-19 pandemic (March 2020), there appeared to be a significant increase in the alcohol intoxication rate of 13.76% ($P < 0.02$, $CI = [2.42-24.91]$).

The trend of alcohol intoxication after the COVID-19 pandemic (relative to the pre-COVID-19 trend) decreased by 1.44% per month, which was not statistically significant ($P = 0.05$, $CI = [-2.91 to 0.02]$).

In addition, after the COVID-19 pandemic, alcohol intoxication decreased by 1.41% per month. This decrease was not statistically significant ($P = 0.06$, $CI = [-2.84 to 0.02]$).

Alcohol-related mortality. As shown in Table 3 and Fig. 4, the alcohol-related mortality rate decreased every month before March 2020 by 0.01%. This decrease was not statistically significant ($P = 0.47$, $CI = [-0.05 to 0.02]$).

In the first month of the COVID-19 pandemic (March 2020), there appeared to be a significant increase in the alcohol intoxication mortality rate of 8.50% ($P = 0.001$, $CI = [3.54 to 13.47]$). The trend of alcohol intoxication after the COVID-19 pandemic (relative to the pre-COVID-19 trend) decreased by 0.73% per month, which was statistically significant ($P = 0.02$, $CI = [-1.35 to -0.10]$). In addition, after the COVID-19 pandemic, alcohol intoxication decreased by 0.74% per month. This decrease was statistically significant ($P = 0.02$, $CI = [-1.36 to -0.12]$).

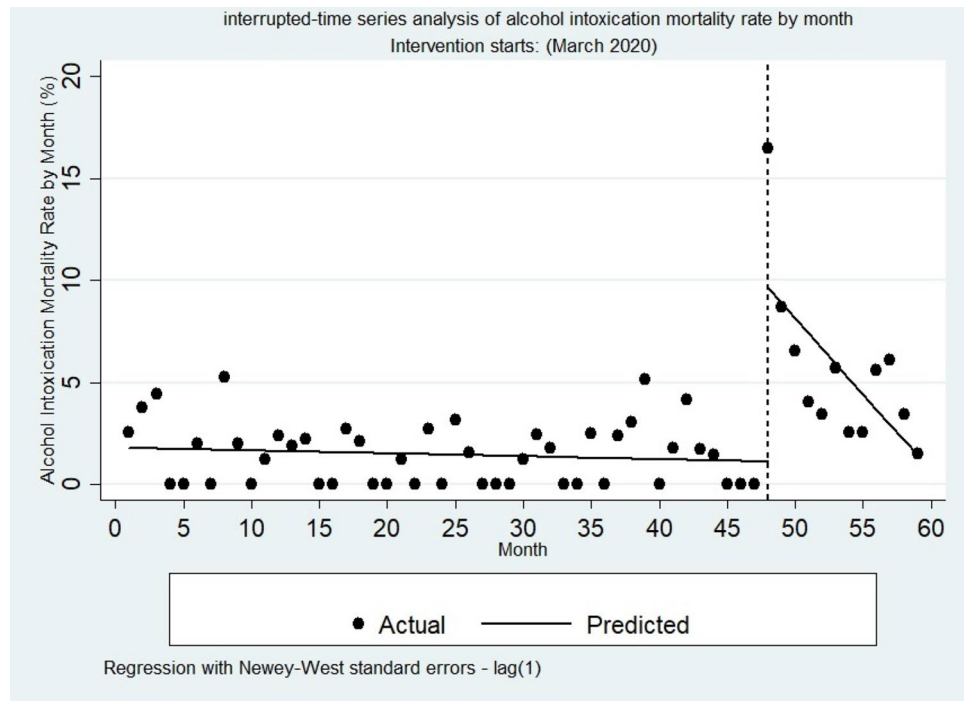


Figure 4. Interrupted time series of alcohol-related mortalities by month.

Discussion

As far as we know, this study reports the highest number of methanol poisoning cases in a single center in the world addressing the trend of alcohol intoxication before and after COVID-19 pandemic^{29,30}. Based on our results, a rough twofold increase is detected in the number of alcohol poisoned cases during the pandemic. In addition, there was a discernible rise in the first 3 months after the beginning of the outbreak. During the pandemic, people experienced numerous adversities in their lives including lockdowns and social distancing, distant working, unemployment, loss of the family, and school closures³¹. During the early days of the pandemic, it was challenging for many people to come up with a variety of stressful stimuli including the fear of the disease and uncertainty about the future³². Studies have reported increased anxiety and distress in several countries^{33,34}. Increasing alcohol consumption was a coping behavior to this elevated anxiety³². Evidence shows dramatic increase in the alcoholic beverages sales^{35,36} even though several countries utilized restrictive measures to control alcohol consumption²⁴.

Working from home needs adjustment in daily routines and consequently causes an elevated anxiety state³⁴. Unemployment acted similarly and resulted in higher alcohol consumptions³². Evidence from former economic crises also highlights similar consequences³⁷. In such situation, despite being unemployed, people may tend to use cheap alcoholic beverages in a cost-saving manner³⁸. Solitary drinking is also believed to be a risk factor for deleterious outcomes of alcohol consumption³⁹.

Additionally, patients with COVID-19 infection and their families as well as the health care workers experience stigmatizations resulting in stressful stimuli⁴⁰. There are reports of concomitant COVID-19 infection and methanol poisoning⁴¹. Loss of friends and relatives and complicated grief are of the other factors altering alcohol consumption behavior⁴². Having to provide childcare while working from home also reported to be stressful for the parents during the pandemic^{29,31}. Lockdown and restrictive measures have also made school and university student another vulnerable group; it shown that interactions with teachers and classmates have a fundamental role in reducing mental health problems including anxiety and depression⁴³.

The pandemic has also been associated with an increase in depression in the public⁴⁴. Many people with psychological and mental disorders may be deprived from obtaining appropriate care due to the fear of becoming infected or reduced resources due to restrictive measures³¹.

In crises, people seek for new information to be up to date from any source possible which may predispose the society to the danger of false information and rumors². Based on our results, during the first 3 months of the outbreak, a discernible rise was spotted in the number of alcohol-poisoned cases and specifically in the numbers of methanol-poisoned patients. It was erroneously propagated that alcohol prevented COVID-19 infection. People started to drink alcoholic beverages and even sanitizers to prevent infection. On the other hand, increased demand for hand sanitizers led to scarcity and finally indulgence of the market with low-quality products containing methanol⁴⁵.

The increased risk of poisoning was detected in all age groups. It was initially believed that alcohol poisoning was more suicidal or deliberate among adults and adolescents and more accidental among children⁴⁶. However,

our results showed that even in the adults it was more recreational. This could also be due to stocking of low-quality alcohol-containing products and sanitizers at homes.

In Iran, alcohol drinking is prohibited, and the black market provides alcoholic beverages to the public. There is no national center for monitoring alcohol consumption in the society, and data on its sale and use are missing. However, a recent study suggests the rising trend of alcohol poisoning through the recent years⁴⁷. Outbreaks of methanol poisoning in Iran have been occurred frequently and have been always a public health concern^{48–50}. Our data suggests a sharp rise in methanol poisoning in the first 3 months after the outbreak resulting in high mortality in the total population and specifically among adolescents. Of seven deceased adolescents, methanol poisoning was diagnosed in six, all happening in those 3 months. Another fact is that methanol poisoning regularly peaked during the year preceding the COVID-19 epidemic but after that it never reached a zero level. This is another concern implying the fact that the market is continuously indulged with low-quality products resulting in ongoing methanol poisoning.

Due to the prohibition of alcohol consumption and legal consequences, intoxicated people usually avoid referring to the health care facilities until the final stages of the poisoning resulting in a higher mortality and morbidity⁵¹. This emphasizes the importance of active case finding⁵².

Limitations. Considering the retrospective nature of the study, we could not retrieve the intent of alcohol ingestion in many cases; also, we were not able to follow the patients after discharge to check for possible mortality post-discharge. The generalizability of this single-center study is unclear. The current study may be subject to selection bias, as we did not measure methanol and ethanol levels of all poisoned patients. Measurement was done only in those with a history of alcohol ingestion or clinical finding/lab exams in favor of alcohol intoxication.

Conclusion

Market surveillance and increasing public awareness should be intensified to prevent further methanol poisonings during the COVID-19 epidemic in Iran. Public education on dangerous effects of non-standard alcoholic beverages and sanitizers as well as proper stocking of these products at home can decrease alcohol poisonings in all age groups.

Measures to control alcohol consumption and suicidal attempts should be followed more intensely among adolescents and social support should be provided for this age group especially during crises of this kind as more risky behaviors are anticipated in them⁵³. This is extremely important as their drinking habit in this period may affect their drinking habit as an adult^{54,55}.

It should be borne in mind that monitoring and measures should not be limited to the pandemic era. Previous experiences from the SARS epidemic⁵⁵ and the economic crisis of 2007–2008⁵⁶ showed a delayed increase in the trend of alcohol consumption in the following years which should be foreseen and avoided by implementation of adequate preventive measures.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 11 October 2021; Accepted: 13 June 2022

Published online: 22 June 2022

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Acknowledgements

The authors wish to thank Alireza Shamsi-Lahijani the medical student of Shahid Beheshti University of Medical Sciences, for his assistance in data collection. Also, we are very grateful to Dr. Vali Baigi who ran the interrupted time series analysis and interpreted the results.

Author contributions

O.R., A.A.K. and H.H.M. participated in the study design. N.G., F.F. and S.K.H. participated in the acquisition and interpretation of data. S.K.H. and N.G. checked the accuracy of data. S.K.H. wrote the first draft of manuscript. N.Z., R.M., and H.H.M. critically revised the manuscript. All the authors have read the journal's authorship agreement and the manuscript has been reviewed and approved by all named authors.

Funding

The authors report no relevant disclosures. This study was supported by Shahid Beheshti University of Medical Sciences (award number 33127).

Competing interests

The authors declare no competing interests.

Additional information

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