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Viral hepatitis C: a study on mortality and multiple causes of death

Hepatite viral C: um estudo da mortalidade e das causas múltiplas de morte

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ABSTRACT:
Objective: To describe the deaths recorded on death certificates mentioning hepatitis C among residents in the Federal District between 2006 and 2020. **Methods:** This descriptive epidemiological study used official, non-nominal databases of the Mortality Information System (*Sistema de Informação sobre Mortalidade*). Data analysis was performed with TabWin, Microsoft Excel, and Stata software, alongside population estimates from the Planning Company of the Federal District (*Companhia de Planejamento do Distrito Federal)*. Trend analysis was conducted using Prais-Winsten linear regression. **Results:** Between 2006 and 2020, 487 deaths mentioning hepatitis C were recorded. Among these, 229 (47.0%) listed hepatitis C as the underlying cause, while 258 (53.0%) identified hepatitis C solely as an associated cause. The overall mortality rates for hepatitis C and the adjusted mortality rates (hepatitis C + hepatocellular carcinoma) showed stationary trends. **Conclusion:** Hepatitis C was underreported as the underlying cause of death. This underscores the need for professional training and a review of the criteria used to determine the underlying cause of mortality.

Keywords: Viral Hepatitis C; Mortality; Multiple causes of death.

RESUMO:
Objetivo: descrever os óbitos com menção da hepatite C na declaração de óbito, de residentes no Distrito Federal, ocorridos no período de 2006 a 2020. **Método:** Estudo epidemiológico descritivo a partir dos bancos de dados oficiais, não nominais, do Sistema de Informação sobre Mortalidade. Foram utilizados os *softwares TabWin,* Microsoft Excel e Stata e as estimativas populacionais da Companhia de Planejamento do Distrito Federal e realizada a regressão linear de Prais-Winsten. **Resultados:** Entre 2006 e 2020, foram registrados 487 óbitos com menção de hepatite C, 229 (47,0%) tiveram a hepatite C como causa básica e 258 (53,0%) tiveram a hepatite C apenas como causa associada. As taxas de mortalidade geral por hepatite C e por hepatite C mais carcinoma apresentaram tendências estacionárias. **Conclusão:** A hepatite C foi submensurada como causa básica de morte. Há necessidade de capacitar os profissionais e revisar as regras de seleção da causa básica de mortalidade.

Palavras-chave: Hepatite C; Mortalidade; Causas múltiplas de morte.

INTRODUCTION

Viral hepatitis is an inflammatory process of the liver caused by viruses identified as A, B, C, D (Delta), and E. Viral hepatitis C (HCV), the focus of the present study, triggers immune responses that, if unsuccessful in eliminating the virus during the acute phase of infection, can result in viral persistence and progression to the chronic phase of the disease.[1,2] In the chronic phase, the virus continues to replicate within the liver, potentially leading to progressive damage. Without treatment, approximately 20% of patients with chronic HCV develop liver cirrhosis, a condition characterized by the replacement of normal liver tissue with scar tissue, which can lead to severe complications such as hepatic failure and liver cancer.[3]

After the diagnosis of liver cirrhosis, the annual risk of developing hepatocellular carcinoma (HCC) ranges from 1% to 5%.[3] The annual risk of liver decompensation, an imbalance of liver functions characterized by variceal hemorrhage, ascites, and/or hepatic encephalopathy, all caused by portal hypertension,[4] is estimated to occur in 3% to 6% of cases. Following the initial episode of hepatic decompensation, the risk of mortality within the subsequent 12 months ranges from 15% to 20%.[5]

In 2019, the global incidence of acute HCV was 73.9 cases per 100,000 inhabitants, with a mortality rate of 0.07 deaths per 100,000 people.[6] In Brazil, from 2000 to 2022, the Ministry of Health reported 298,738 confirmed cases of HCV through the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – Sinan). The incidence rate in 2022 was 6.6 cases per 100,000 inhabitants nationwide and 4.3 cases per 100,000 inhabitants in the Federal District.[7] Regarding mortality, HCV represents the leading cause of death among viral hepatitis cases in Brazil. In 2021, the nationwide mortality rate from HCV was 0.5 deaths per 100,000 inhabitants, while in the Federal District, it was 0.6 deaths per 100,000 inhabitants.[7] However, it is important to note that deaths listing HCV as an underlying cause are likely underreported in the information system due to the complexity of the clinical presentation and disease progression toward death. Consequently, there is a pressing need for enhanced depth and accuracy in studying this data to facilitate a comprehensive analysis of the health situation in affected regions.

Mortality statistics are globally presented based on the underlying cause of death,[8] defined as "*the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.*" [9] However, for a comprehensive mortality study, all causes present at the time of death or contributing to the outcome should be documented in the death certificate (DC).[10] Despite the worldwide adoption of a standardized DC model and a precise definition of the underlying cause, mortality statistics have historically been inaccurate. According to Martins RC and Buchalla CM (2015),[11] errors may occur during the coding process of causes of death, compromising the quality of mortality data. One potential error stems from physicians' documentation of causes, leading to coding inaccuracies due to insufficient disease specification. Another potential error lies in the selection of the underlying cause, given the complexity and comprehensiveness of the selection rules. Consequently, analyses based solely on underlying cause data may fail to fully acknowledge the epidemiological significance of certain diseases.

Therefore, investigations, analyses, or even basic tabulations of the diverse diseases or health conditions and their complications documented at the time of death, as reported in the DC, are referred to as studies of 'multiple causes of death.'[12] This term encompasses the entirety of underlying and associated causes listed in the DC. Associated causes include both consequential and contributing factors.[13,14]

Consequential causes are those that result from the underlying cause, representing complications or consequences. They are documented in Part I of the DC above the

underlying cause. Contributing causes, on the other hand, are additional pathological conditions that contributed to death but did not form part of the chain initiated by the underlying cause. These are reported in Part II of the DC.[12–14]

Between 2017 and 2021, the Mortality Information System (*Sistema de Informação sobre Mortalidade* – SIM) reported 109 deaths (34.9%) in the Federal District (DF) where any form of viral hepatitis was listed as the underlying cause. During the same period, 203 deaths (65.1%) were recorded, where viral hepatitis was cited as an associated cause.[15,16] The underlying cause is used to calculate the mortality rate, an indicator that estimates the risk of mortality from a specific disease and assesses its significance as a public health concern.[18] Specifically concerning HCV, the mortality rate may not fully reflect the disease's impact on population mortality since it is often cited in DCs as an associated cause in a large proportion of deaths attributed to other underlying causes.

Therefore, the present study aims to delineate deaths attributed to HCV in the Federal District from 2006 to 2020 by analyzing the multiple causes of death, thereby revealing the extent of HCV's contribution to mortality records. Investigating HCV-related deaths and disseminating information on mortality indicators will aid in shaping public health policies aimed at preventing the disease and its consequences, as well as mitigating undesirable outcomes such as treatment costs and mortality.

METHODOLOGY

STUDY TYPE

This study is a descriptive epidemiological analysis of death records attributed to HCV, involving analyses of individual and temporal characteristics, as well as ecological analyses spanning the years 2006 to 2020. It encompasses death records of individuals residing in the Federal District.

STUDY POPULATION

The study population comprises individuals who passed away between January 1, 2006, and December 31, 2020, with mention of HCV in their DCs and who were residents of the Federal District.

INCLUSION CRITERIA

Deaths attributed to HCV were included based on the presence of the following International Classification of Diseases (ICD-10) codes on any line of the DC: B17.1 (acute HCV) or B18.2 (chronic HCV).

DATA SOURCE

The study utilized secondary data sourced from official, non-nominal repositories of the SIM, accessible via the database of the Health Information and Situation Analysis Management (*Gerência de Informação e Análise da Situação de Saúde* – GIASS), the district manager of SIM.

DATA EXTRACTION AND ANALYSIS

Data extraction and analysis were conducted using TabWin, version 4.1.5, structured query language (SQL) module, and Microsoft Excel, version 2019. The overall and specific mortality coefficients for HCV, categorized by sex and age group, were calculated for each year of the study. Descriptive analyses were conducted, considering the absolute and relative frequencies of the evaluated data. Population estimates were sourced from the Planning Company of the Federal District (*Companhia de Planejamento do Distrito Federal* – Codeplan).

For the temporal trend analysis, the mortality coefficients were logarithmically transformed, and the Prais-Winsten linear regression was applied to estimate the beta values (b1) along with their 95% confidence intervals (b1 minimum and b1 maximum). Subsequently, the annual percentage change (APC) was calculated using the formula: [(-1+10 ^ b1)*100%] with corresponding 95% confidence intervals [(–1+10 ^ b1 minimum)*100%; (–1+10 ^ b1

maximum)*100%]. The trend was considered to increase when both APC and its 95% CI were positive, decrease when both APC and its 95% CI were negative, and be stationary when APC values were either positive or negative, but the 95% CI included zero. The Durbin-Watson test was used to verify autocorrelation. All analyses were performed using Stata, version 17, serial number 301706385466.

ETHICAL ASPECTS

The project was approved by the Ethics Committee of the Foundation for Teaching and Research in Health Sciences of the Federal District Health Department (*Fundação de Ensino e Pesquisa em Ciências da Saúde da Secretaria de Estado de Saúde do Distrito Federal* – FEPECS/SES/DF) – Opinion Number 5.373.529, dated April 27, 2022.

RESULTS

OVERVIEW OF THE DISTRIBUTION OF DEATHS

Between 2006 and 2020, 487 deaths mentioning HCV were recorded in the SIM, on any line of the DC, among residents of the Federal District. Of these deaths, 229 (47.0%) listed HCV as the underlying cause, while 258 (53.0%) listed HCV only as an associated cause.

Of the total deaths analyzed, 458 (94%) were related to chronic HCV and 29 (6%) to acute HCV. The ratios between the frequency of mentions and frequency of underlying causes of chronic and acute HCV were 2.1 and 2.2, respectively.

HCV AS THE UNDERLYING CAUSE

In the 229 DCs where HCV was recorded as the underlying cause, 666 consequential causes were mentioned. Among these, the most frequent were "other and unspecified cirrhosis of the liver' (K74.6), 'sepsis' (A41.8 + A41.9), and 'acute, chronic or unspecified hepatic failure' (K72.0 + K72.1 + K72.9), with 142 (21.3%), 73 (11.0%), and 60 (9.0%) mentions, respectively. Table 1 details the 20 most frequent consequential causes.

Among the contributing causes listed on DCs where HCV was the underlying cause, the most frequent were 'non-insulin-dependent or unspecified diabetes mellitus' (E11.2 + E11.9 + E14.2 + E14.8 + E14.9), 'acute, chronic or unspecified renal failure' (N17.9 + N18.9 + N1.9), and 'essential (primary) hypertension' (I10), with 21 (10.3%), 21 (10.3%), and 18 (8.9%) mentions, respectively. Notably, among the deaths where HCV was the underlying cause, chronic HCV was mentioned in Part II of 42 DCs.

Table 1. Distribution of the most frequent consequential causes, according to ICD-10, in death certificates with viral hepatitis C listed as the underlying cause of death. Federal District, 2006–2020.

Viral hepatitis C listed as the underlying cause of death and consequential causes			
Description	**ICD-10 Code**	**N**	**%**
Other and unspecified cirrhosis of the liver	K74.6	142	21.3
Sepsis	A41.8	73	11.0
Acute or chronic liver failure or without other specifications	K72.0 + K72.1 + K72.9	60	9.0
Cardiogenic or hypovolemic or unspecified shock	R57.0 + R57.1 + R57.8 + R57.9	42	6.3
Hematemesis	K92.0	37	5.6
Other specified general symptoms and signs	R68.8	33	5.0
Bacterial or unspecified pneumonia	J15.8 + J15.9 + J18.9	30	4.5
Acute, chronic, or unspecified renal failure	N17.9 + N18.9 + N19	24	3.6
Esophageal varices	I85.0 + I85.9	23	3.5
Acute respiratory distress or unspecified	J96.0 + J96.9	19	2.9

Viral hepatitis C listed as the underlying cause of death and consequential causes			
Description	**ICD-10 Code**	**N**	**%**
Hepatorenal syndrome	K76.7	15	2.3
Acute or unspecified peritonitis	K65.0 + K65.9	13	2.0
Gastrointestinal bleeding not otherwise specified	K92.2	13	2.0
Liver disease not otherwise specified	K76.9	8	1.2
Pneumonitis due to food or vomiting	J69.0	7	1.1
Portal hypertension	K76.6	7	1.1
Ascites	R18	7	1.1
Abnormal reactions in patients or late complications caused by surgical intervention	Y83.0 + Y83.9	7	1.1
Acidosis	E87.2	5	0.8
Unspecified heart failure	I50.9	5	0.8
Other causes	*	96	14.4
Total	*	**666**	**100.0**

Source: SIM
*Various ICD-10 codes.

HCV AS AN ASSOCIATED CAUSE

In the analysis of the 258 deaths where HCV was an associated cause, the underlying causes most frequently identified by the Underlying Cause Selection (*Seletor de Causa Básica* – SCB) System were 'hepatocellular carcinoma or malignant neoplasm of the liver, unspecified' (C22.0 + C22.9), 'human immunodeficiency virus [HIV] disease resulting in other infections' (B20.0 + B20.3 + B20.7 + B22.7 + B23.8), and 'alcoholic cirrhosis of liver' (K70.3), with 84 (32.6%), 50 (19.4%), and 20 (7.8%) mentions, respectively (Table 2).

The most frequently mentioned contributing causes on DCs listing HCV as an associated cause were 'acute or chronic viral hepatitis C' (B17.1 + B18.2), 'human immunodeficiency virus [HIV] disease resulting in other viral infections' (B20.3 + B2.4), and 'mental and behavioral disorders due to the use of alcohol or other drugs' (F10.1 + F10.2 + F14.2 + F17.2 + F17.9 + F19.7), with 151 (41.3%), 24 (6.6%), and 24 (6.6%) mentions, respectively.

Table 2. Distribution of viral hepatitis C listed in death certificates as an associated cause of death according to the 20 most frequent underlying causes, selected by the BCS, using ICD-10. Federal District, 2006–2020.

Hepatitis C as an associated cause of death (258) and the 20 most frequent underlying causes			
Description	**ICD-10 Code**	**N**	**%**
Hepatocellular carcinoma or malignant neoplasm of the liver, unspecified	C22.0 + C22.9	84	32.6
HIV disease resulting in other infections	B20.0 + B20.3 + B20.7 + B22.7 + B23.8	50	19.4
Alcoholic liver cirrhosis	K70.3	20	7.8
Diabetes mellitus	E10.1 + E10.7 + E11.2 + E11.5 + E14.2 + E14.5 + E14.9	8	3.1
Hypertensive kidney disease with renal failure	I12.0	5	1.9
Chronic or unspecified renal failure	N18.9 + N19	5	1.9
Cerebrovascular accident, unspecified as hemorrhagic or ischemic	I64	4	1.6

Hepatitis C as an associated cause of death (258) and the 20 most frequent underlying causes			
Description	**ICD-10 Code**	**N**	**%**
Chronic obstructive pulmonary disease	J44.0 + J44.9	4	1.6
Coronavirus infection of unspecified location	B34.2	3	1.2
Unspecified intracerebral hemorrhage	I61.9	3	1.2
Falls at the same level	W18.5 + W18.9	3	1.2
Chagas disease (chronic) with impairment of the digestive tract	B57.3	2	0.8
Malignant neoplasm of rectum	C20	2	0.8
Malignant neoplasm of pancreas, unspecified	C25.9	2	0.8
Malignant neoplasm of breast, unspecified	C50.9	2	0.8
Non-Hodgkin's lymphoma of unspecified type	C85.9	2	0.8
Sickle cell anemia without crisis	D57.1	2	0.8
Unspecified acute myocardial infarction	I21.9	2	0.8
Congestive or unspecified heart failure	I50.0 + I50.9	2	0.8
Alcoholic hepatic failure	K70.4	2	0.8
Other causes	*	51	19.8
Total	*	**258**	**100.0**

Source: SIM
*Various ICD-10 codes.

MORTALITY INDICATORS, DESCRIPTION, AND TIME SERIES ANALYSIS

The highest mortality rate from HCV as the underlying cause was 1.0 deaths per 100,000 inhabitants, recorded in 2006, while the lowest was 0.4 deaths per 100,000 inhabitants, recorded in 2007, 2010, 2014, 2015, and 2017. For males, the highest mortality rate was 1.6 deaths per 100,000 inhabitants in 2006, and the lowest was 0.2 deaths per 100,000 inhabitants in 2007. For females, the highest mortality rate was 0.6 deaths per 100,000 inhabitants in 2007, and the lowest was 0.2 deaths per 100,000 inhabitants in 2020 (Figure 1).

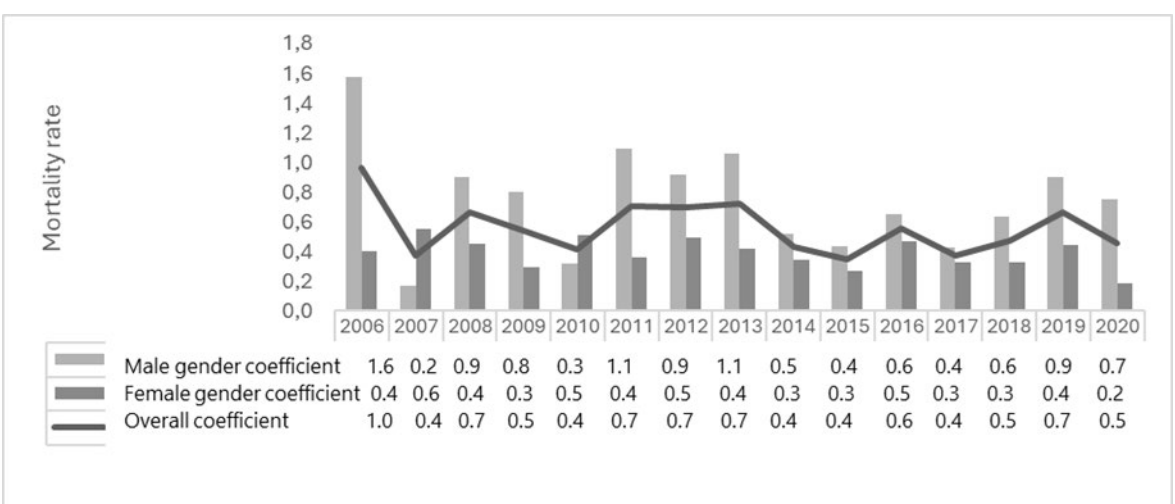

Figure 1. Distribution of deaths from viral hepatitis C listed as the underlying cause of death according to the mortality rate by cause and gender (per 100,000 inhabitants). Federal District, 2006–2020.
Source: SIM

The highest mortality rates were found in the age group of 50 years and over. In the age group of 50–69 years, the highest mortality rate was 5.6 deaths per 100,000 inhabitants in 2006, and the lowest was 0.6 deaths per 100,000 inhabitants in 2017. In the age group of 70 years and over, the highest mortality rate was 9.8 deaths per 100,000 inhabitants in 2008, and the lowest was 0.7 deaths per 100,000 inhabitants in 2020.

When deaths from HCV were analyzed in combination with HCC (ICD 10 – C220), unspecified malignant neoplasm of the liver (ICD 10 – C229), and other specified carcinomas of the liver (ICD 10 – C227) as the underlying cause, there were 314 records in the period. The highest mortality rate was 1.1 per 100,000 inhabitants in 2006, and the lowest was 0.5 per 100,000 inhabitants in 2007 (Table 3). The mortality rate in males varied from 1.8 deaths per 100,000 inhabitants in 2006 to 0.3 deaths per 100,000 inhabitants in 2007. The highest female mortality rate was 0.6 per 100,000 inhabitants in 2007, 2008, 2010, 2011, 2012, and 2019, and the lowest was 0.3 deaths per 100,000 inhabitants in 2020 (Table 3).

In the age group of 50–69 years, the mortality rate ranged from 5.6 deaths per 100,000 inhabitants in 2006 to 1.8 deaths per 100,000 inhabitants in 2007. In the age group of 70 years and over, the highest mortality rate was 12.7 deaths per 100,000 inhabitants in 2006, and the lowest was 1.3 deaths per 100,000 inhabitants in 2009 (Table 3).

Table 3. Distribution of deaths from viral hepatitis C listed as an underlying cause or hepatocellular carcinoma or malignant neoplasm of the liver, unspecified, or other specified carcinomas of the liver, according to year of registration, mortality rate by cause, and mortality rate by gender and age group. Federal District, 2006–2020.

Year	Geral		Male		Female		20-29 years		30-49		60-69 years		≥70 years	
	N	rate	N	rate	N	rate	N	rate	N	rate	N	rate	N	rate
2006	26	1.1	20	1.8	6	0.5	1	0.2	6	0.9	13	5.6	6	12.7
2007	11	0.5	4	0.3	7	0.6	0	0	2	0.3	5	1.8	4	6.1
2008	20	0.8	12	1	8	0.6	0	0	3	0.4	9	2.9	8	11.2
2009	16	0.6	11	0.9	5	0.4	0	0	3	0.4	12	3.8	1	1.3
2010	16	0.6	8	0.6	8	0.6	1	0.2	3	0.4	8	2.3	4	5
2011	23	0.9	15	1.2	8	0.6	1	0.2	6	0.7	11	3.1	5	5.9
2012	24	0.9	16	1.2	8	0.6	1	0.2	3	0.3	17	4.5	3	3.3
2012	27	1	20	1.5	7	0.5	0	0	7	0.8	15	3.8	5	5.3
2014	20	0.7	12	0.9	8	0.5	0	0	2	0.2	16	3.8	2	2
2015	23	0.8	16	1.2	7	0.5	0	0	4	0.4	14	3.2	5	4.7
2016	21	0.7	14	1	7	0.5	0	0	2	0.2	17	3.7	2	1.8
2017	18	0.6	12	0.9	6	0.4	0	0	4	0.4	9	1,9	5	4.2
2018	21	0.7	15	1.1	6	0.4	0	0	1	0.1	12	2.4	8	6.4
2019	26	0.9	17	1.2	9	0.6	0	0	2	0.2	17	3.3	7	5.2
2020	22	0.7	18	1.2	4	0.3	0	0	0	0	19	3.5	3	2.1
Total	**314**	*	**210**	*	**104**	*	**4**	*	**48**	*	**194**	*	**68**	*

Source: SIM

When comparing the mortality rates of deaths where hepatitis C was the underlying cause with those of deaths where hepatitis C, hepatocellular carcinoma, unspecified malignant liver neoplasm, or other specified liver carcinomas were the underlying causes, the

difference between these latter indicators and the former ranged from 0.1 death per 100,000 inhabitants (in 2006, 2007, 2008, 2009, and 2011) to 0.5 death per 100,000 inhabitants (in 2015).

Mortality rates due to HCV as an underlying cause, in general, for males and the groups of 50–69 and 70 years and over showed stationary trends evidenced by the annual growth rates. Trends for females and the age group of 30–49 years decreased. The trends exhibited similar behavior for mortality rates from HCV combined with carcinoma (Table 4).

Table 4. Annual rate of increase regarding mortality from viral hepatitis C as underlying cause and mortality from viral hepatitis C as underlying cause or hepatic cell carcinoma or malignant neoplasm of the liver, unspecified, or other specified carcinomas of the liver and subgroups. Federal District, 2006–2020.

Variable	% Increment	95% CI	Trend
Overall mortality from hepatitis C	-4.18	(-10.89 to 3.04)	Stationary
Mortality from hepatitis C in males	1.67	(-9.62 to 14.37)	Stationary
Mortality from hepatitis C in females	-6.24	(-10.05 to -2.27)	Decreasing
Mortality from hepatitis C in the age group of 30–49 years	-13.18	(-23.14 to -1.94)	Decreasing
Mortality from hepatitis C in the age group of 50–69 years	-8.58	(-20.09 to 4.59)	Stationary
Mortality from hepatitis C in the age group of 70 years and over	-18.9	(-35.81 to 2.46)	Stationary
Overall mortality from hepatitis C + carcinoma	0.21	(-5.36 to 6.11)	Stationary
Mortality from hepatitis C + carcinoma in males	7.92	(-0.23 to 16.73)	Stationary
Mortality from hepatitis C + carcinoma in females	-4.95	(-8.24 to -1.54)	Decreasing
Mortality from hepatitis C + carcinoma in the age group of 30–49 years	-17.13	(-25.14 to -8.27)	Decreasing
Mortality from hepatitis C + carcinoma in the age group of 50–69 years	-1.36	(-9.35 to 7.33)	Stationary
Mortality from hepatitis C + carcinoma in the age group of 70 years and over	-10.75	(-22.87 to 3.28)	Stationary

Source: SIM

DISCUSSION

HCV infection was identified as the underlying cause of 47.0% of total deaths, in which HCV was mentioned during the analyzed period. According to Lenice Ishitani and Elizabeth França (2001),[19] the analysis focusing on multiple causes of death for HCV in the Federal District is indicated since the ratio of mentions to underlying causes was greater than two,[19] underscoring the relevance of the present study. A study conducted in Massachusetts, USA, also demonstrated that HCV-related deaths are underestimated when analyzed solely based on the underlying cause of death. [20] The authors highlight the magnitude of the problem when utilizing the multiple causes of death methodology for analysis.

Among the deaths for which HCV was listed as the underlying cause, chronic HCV was mentioned in Part II of 42 DCs, indicating that the underlying cause selected by the SCB may have differed from the physician's intended report. This discrepancy suggests a possible error in completing the DCs.

It is also noteworthy that of the 29 DCs mentioning acute HCV, 11 included the code K746, referring to 'other and unspecified cirrhosis of the liver,' and five listed the code C220, referring to 'hepatocellular carcinoma.' The presence of codes referring to chronic processes raises the hypothesis that part of these mentions of acute HCV is due to coding errors, which would

further reduce the percentage of deaths from acute HCV.

A.E.S. Sehdev and G.M. Hutchins (2001)[21] analyzed 494 DCs that listed various causes of death and found that more than 40% of the DCs contained incorrectly filled-in causes. Some of the most common errors made by physicians included listing the underlying and immediate causes of death out of order and placing underlying or immediate causes of death in Part II.[21]

Among the deaths with HCV as only an associated cause, the most frequently selected underlying causes were 'hepatocellular carcinoma or malignant neoplasm of the liver, unspecified' (C220 + C229), 'human immunodeficiency virus [HIV] disease resulting in other infections' (B200 + B203 + B207 + B227 + B238), and 'alcoholic cirrhosis of liver' (K703). Among the deaths with HCV as the underlying cause, the most frequent consequential causes were 'other and unspecified cirrhosis of the liver' (K746), 'sepsis' (A418 + A419), and 'acute, chronic or unspecified hepatic failure' (K720 + K721 + K729).

Similarly, HCC, liver cirrhosis, and alcohol-related liver disease were among the most frequent causes in a cross-sectional study conducted in the United States in 2010. [22] The authors found that among HCV deaths, the most frequently mentioned multiple causes of death (including underlying, intermediate, immediate, and contributing causes) were fibrosis, cirrhosis, and other liver diseases (48.4%); liver cancer, including HCC and intrahepatic bile duct cancer (17.0%); alcohol-related liver disease (16.5%); substance-related mental disorders (14.0%); cardiac arrest and ventricular fibrillation (10.6%); uncomplicated diabetes mellitus (10.2%); and essential hypertension (9.8%).

In the present study, among the deaths where HCV was listed as only an associated cause, the most frequent underlying cause was liver cancer, with 84 deaths having either C220 (HCC) or C229 (malignant neoplasm of the liver, unspecified) as the underlying cause. It is worth noting that even when Part I of the DC was filled out with a natural sequence of events—such as B182 (chronic HCV) on line C, K746 (other and unspecified cirrhosis of the liver) on line B, and C220 (HCC) on line A—the SCB selected C220 as the underlying cause.

The SCB's explanation indicates that neither B182 nor K746 causes C220. Additionally, it reports that rule 2 was used to select the underlying cause. This rule states that when there is no sequence of events that ends in the condition mentioned first in the DC, the underlying cause selected must be the condition mentioned in the first line of Part I of the DC.[9] A similar situation arises when code C220 is replaced with code C229 (malignant neoplasm of the liver, unspecified). According to ICD-10, HCV does not cause liver cancer (C220 or C229). Thus, even when HCV is correctly declared as the underlying cause (last line filled in Part I), it is ruled out by the SCB in favor of cancer. However, since HCC can be a consequence of chronic HCV, according to the concept of the underlying cause, HCV should be selected as the underlying cause in this sequence of events.

A case-control study conducted in the United States concluded that HCV is associated with an increased risk of liver cancers (adjusted odds ratio [aOR] = 31.5; 95% confidence interval [CI], 29.0-34.3) in the elderly US population; the study also found an increased risk for other cancers, mainly intrahepatic bile duct cancers (aOR, 3.40; 95% CI, 2.52-4.58), extrahepatic bile duct cancers (aOR, 1.90; 95% CI, 1.41-2.57), and diffuse large B-cell lymphoma (aOR, 1.57; 95% CI, 1.34-1.84).[23] Therefore, it was found that chronic hepatitis C might have been underestimated as the underlying cause in favor of liver cancer (C220 or C229) in deaths where the certifying physician indicated a causal relationship between chronic HCV and HCC.

In the present study, other underlying causes frequently selected among deaths where HCV was only an associated cause included alcoholic cirrhosis of the liver (K70.3), alcoholic hepatic failure (K70.4), and alcoholic hepatitis (K70.1). However, it is known that HCV also contributes to the development of liver disease in these patients. Therefore, attributing liver damage to one cause or another in isolation may be erroneous. Ideally, there should be an ICD-10 code that describes the pathology resulting from the combined action of alcohol and HCV. Even replacing codes referring to alcohol with a code for unspecified liver disease would lead to the loss of valuable information that could improve the quality of mortality statistics.

A 2011 review article[24] discussed the association between alcohol and HCV, describing how chronic consumption of alcoholic beverages can alter the natural history of chronic hepatitis C by accelerating fibrosis and increasing the risk of cirrhosis and HCC. Ethanol facilitates virus replication and exacerbates HCV-related damage by causing additional harm. Conversely, HCV can worsen and influence the progression of alcoholic liver disease (ALD).[24] Thus, concomitant HCV infection and alcohol abuse act synergistically, leading to more severe liver disease.[25]

A study conducted in California, USA, in 2005 reported higher hospital mortality in patients with both alcoholism and HCV infection compared to patients with alcoholism without HCV (4.4% vs 2.4%, $p < 0.01$).[26] A 2002 study in England linked a sharp increase in mortality (243%) among abusive alcohol users to a concurrent increase in the incidence of HCV during the same period.[27] Another study in 2011 demonstrated that HCV-positive patients with acute alcoholic hepatitis had eight times the risk of dying compared to HCV-negative patients with acute alcoholic hepatitis.[28]

It was noted once again that HCV may be underreported as an underlying cause in favor of alcoholic liver diseases due to the absence of an ICD code that describes liver disease caused by the combined effects of HCV and alcohol.

According to the World Health Organization (WHO), about 30% of deaths due to HCV are attributable to complications of chronic HCV infection, specifically decompensated cirrhosis and HCC. Therefore, the organization includes deaths from HCC and decompensated cirrhosis, in addition to deaths from HCV as the underlying cause, when calculating HCV-related mortality indicators.[29] To eliminate viral hepatitis as a public health problem by 2030, the WHO has set a target to reduce mortality associated with hepatotropic virus infections by 65% compared to 2015.[30] Additionally, the aim is to achieve an annual HCV-related mortality rate of ≤2 per 100,000 inhabitants by 2030.[29]

In the analysis of deaths from HCV combined with HCC (ICD-10: C22.0), unspecified malignant neoplasm of the liver (ICD-10: C22.9), and other specified carcinomas of the liver (ICD-10: C22.7) as the underlying cause, the highest overall mortality rate related to HCV was 1.1 deaths per 100,000 inhabitants in 2006, while the lowest was 0.5 deaths per 100,000 inhabitants in 2007. Throughout the study period, this indicator remained below 2 per 100,000 inhabitants, consistently meeting the absolute target established by the WHO. In the time series analysis of the entire study period, both the mortality rate for HCV and the mortality rate for HCV combined with carcinoma showed stationary trends. Since 2015, the introduction of direct-acting antivirals in the treatment of HCV in Brazil's Unified Health System (SUS) has shown promise, with over 90% rates of sustained virological response.[31–33] As a result, these trends are expected to decline in the coming years. This decline has already been observed in time series analyses for other Brazilian states[34]. Consequently, mortality rates are anticipated to meet the WHO's relative target of reducing mortality associated with hepatotropic virus infections by 65% by 2030.

In the context of the practical implications of this study on HCV deaths in the Federal District using a multiple-cause approach, it is essential to consider how the results can inform public health policies and clinical practices. Understanding the interrelationship between different causes of death can guide the effective allocation of health resources, prioritizing areas where intervention is most needed.

Furthermore, by recognizing multiple contributing causes of death, health professionals can improve the accuracy of mortality records and reports, which is crucial for monitoring epidemiological trends and developing targeted preventive strategies. This approach can enhance clinical practice by promoting a more comprehensive evaluation of the health-disease-care continuum facilitating preventive interventions to address risk factors. Additionally, an integrated and collaborative approach to public health management can reduce mortality rates and contribute to increased population longevity.

CONCLUSION

The present study innovates by employing a multiple-cause approach to analyze

deaths mentioning HCV among residents of the Federal District. This novel perspective has led to more accurate data on HCV-related deaths and has deepened the understanding of the basic and associated causes of death among people living with HCV. This knowledge benefits health managers and professionals in designing and implementing actions and measures to minimize HCV-related complications that result in death in the Federal District.

While the current study faced limitations typically associated with mortality studies using secondary data, such as inadequate completion of DCs and underreporting of deaths, there were notable strengths. The SIM database generally demonstrated excellent completeness of most variables, and the processing of DCs was conducted by a trained team from the SES-DF.

The findings revealed that HCV was underreported as an underlying cause of death. This underscores the importance of using multiple-causes-of-death analysis for a better understanding of the disease's impact in the Federal District. The study also emphasized the need for additional training for professionals who prepare DCs and a review of the rules for selecting the underlying cause and the SCB system to ensure they more accurately reflect the cause that initiated the other events.

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