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Excess mortality rate associated with hepatitis C virus infection: A community-based cohort study in rural Egypt

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Background & Aims: >80% of people chronically infected with hepatitis C virus (HCV) live in resource-limited countries, yet the excess mortality associated with HCV infection in these settings is poorly documented.

Methods: Individuals were recruited from three villages in rural Egypt in 1997–2003 and their vital status was determined in 2008–2009. Mortality rates across the cohorts were compared according to HCV status: chronic HCV infection (anti-HCV antibody positive and HCV RNA positive), cleared HCV infection (anti-HCV antibody positive and HCV RNA negative) and never infected (anti-HCV antibody negative). Data related to cause of death was collected from a death registry in one village.

Results: Among 18,111 survey participants enrolled in 1997–2003, 9.1% had chronic HCV infection, 5.5% had cleared HCV infection, and 85.4% had never been infected. After a mean time to follow-up of 8.6 years, vital status was obtained for 16,282 (89.9%) participants. When compared to those who had never been infected with HCV in the same age groups, mortality rate ratios (MRR) of males with chronic HCV infection aged <35, 35–44, and 45–54 years were 2.35 (95% CI 1.00–5.49), 2.87 (1.46–5.63), and 2.22 (1.29–3.81), respectively. No difference in mortality rate was seen in older males or in females. The all-cause mortality rate attributable to chronic HCV infection was 5.7% (95% CI: 1.0–10.1%), while liver-related mortality was 45.5% (11.3–66.4%).

Conclusions: Use of a highly potent new antiviral agent to treat all villagers with positive HCV RNA may reduce all-cause mortality rate by up to 5% and hepatic mortality by up to 40% in rural Egypt.

Keywords: Hepatitis C; Mortality; Cohort studies; Egypt; Africa.

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Abbreviations: HCV, Hepatitis C Virus; HCC, Hepatocellular carcinoma; HIV, Human Immunodeficiency Virus; HBV, Hepatitis B Virus; RNA, Ribonucleic acid; PAF, Population attributable fraction; MRR, Mortality rate ratios; PY, Person-years; 95% CI, 95% confidence interval; IQR, Interquartile range.

Introduction

Hepatitis C virus (HCV) infection is an important public health issue. Globally, 115 million people have been infected with HCV, of whom 80 million are chronically infected [1]. Each year, an estimated 700,000 people die from HCV, mainly through liver cirrhosis and/or hepatocellular carcinoma (HCC) [2]. The majority (>80%) of people chronically infected with HCV reside in low- and middle-income countries [1], and Egypt has the highest prevalence of chronic HCV infection, estimated at 10.0% in adults [3].

With the recent advent of new antiviral therapy which is expected to cure more than 90% of chronic infection within a short duration [4], Egypt has started treating a large number of infected persons through 23 national treatment centres with a regimen that includes the new antiviral agent sofosbuvir [5]. To assess the population impact of this national treatment programme, it is critical to understand the natural history of chronic HCV infection and the excess mortality associated with chronic HCV infection in the local context before treatment programmes are implemented.

Several cohort studies have examined the impact of HCV infection on all-cause and cause-specific mortality rates in general population [6–16]. However, these studies have been restricted to high income countries. To date there has been no similar study conducted in middle- and low-income countries. Moreover, the estimates from studies conducted in high income countries have limited generalisability to other settings. For example, among people with chronic HCV infection, those who inject drugs – a major route of HCV transmission in Europe and

North America – are thought to have additional causes of increased mortality, such as drug overdose, excessive alcohol intake, and co-infection with HIV or hepatitis B virus (HBV) [7–9,13,14]. In contrast, in resource-limited countries, iatrogenic procedures are the most frequent mode of HCV transmission [17]. In Egypt, the beginning of the HCV epidemic has been associated with the mass parenteral anti-schistosomal treatment campaigns in the 1960s–70s [18], and has since spread through the reuse of medical devices [19]. As a result, in a generalized epidemic, such as the one of Egypt, it is expected that the risk of mortality among HCV-infected in Egypt will be different to that found in high income countries.

We therefore conducted a community-based cohort study in rural Egypt to estimate the all-cause mortality rates according to HCV status: chronic HCV infection (anti-HCV antibody positive and HCV RNA positive), cleared HCV infection (anti-HCV antibody positive and HCV RNA negative) and never infected (anti-HCV antibody negative). In addition, we estimated the fraction of all-cause and liver-related mortality rates attributable to chronic HCV infection (population attributable fraction: PAF).

Patients and methods

Baseline sero-surveys

Community-based sero-surveys for HCV infection were conducted in three rural villages in Egypt. In Sallam, Upper Egypt, all villagers aged ⩾5 years were invited to participate in the sero-survey between 1997–1999 [20–22]. In two villages in the Nile Delta, Aghour El Soughra [22–24] and Zawiat Razin [19,25,26], randomly selected inhabitants aged ⩾5 years were invited to the surveys between 1997–1999 and 2002–2003, respectively. After written informed consent was provided, participants underwent a standardised clinical examination, a blood sample was collected, and a structured interview that assessed socio-demographic status and potential risk factors for HCV transmission was conducted. Participants identified as having a chronic HCV infection were referred to a hepatology clinic for further clinical management, and those eligible and willing to be treated were offered pegylated interferon (PegIFN) and ribavirin [27]. The study was approved by the Institutional Review Board of the Egyptian Ministry of Health and Population, the Assiut University (Assiut, Egypt), and the University of Maryland (Baltimore, USA).

Laboratory assays

Serum samples were transferred and tested at the National Hepatology and Tropical Medicine Research Institute in Cairo. Sera from Sallam and Aghour El Soughra were tested for anti-HCV antibody using a second-generation enzyme immunoassay (Abbott HCV EIA 2.0, Abbott Laboratories, Chicago, IL) and positive samples were confirmed using a recombinant immunoblot assay (RIBA, Chiron, Emeryville, CA). Sera from Zawiat Razin were tested using a third-generation anti-HCV assay (INNOTEST HCV Ab IV, Innogenetics, Ghent, Belgium), followed by a confirmation test using AxSYM HCV version 3.0 (Abbott Laboratories). All sera positive for anti-HCV antibodies were further tested for HCV RNA using a direct in-house reverse transcriptase polymerase chain reaction [28].

Ascertainment of death

Between 2008 and 2009, a team of fieldworkers visited each household in the study villages and interviewed household heads to determine vital status of all the survey participants originally recruited between 1997 and 2003. In case of migration of study participants during this period, the date of migration was recorded. In the case of death of a study participant during the follow-up period, the date of death was ascertained through the death registry held in the primary healthcare centre in each village. If this information was not available through the death registry, the date reported by family members was recorded. In Zawiat Razin, the cause of death was also recorded from the death registry. The cause of death was classified into one of eight categories: liver-related (including HCC), neoplasms (excluding HCC), stroke, heart disease, pulmonary disease, kidney disease, other and unknown causes [11].

Statistical analyses

HCV status at enrolment was treated as a categorical variable (chronically infected, cleared HCV infection and never infected). Baseline characteristics of participants were compared according to each HCV status using Chi-square test for categorical variables and Kruskal-Wallis one-way analysis of variance for continuous variables. The person-years of follow-up were calculated from the date the participants were enrolled in the study to the date of death, migration, or last follow-up, whichever came first. The association between HCV status and all-cause mortality was examined by estimating mortality rate ratios (MRR) using Poisson regression, and adjusted for potential confounding variables: sex, current age, study village, education (ever or never attended school: a proxy for socio-economic status), and comorbidity. Comorbidity was defined as the presence of any of the following medical history at enrolment: ⩾2 episodes of blood transfusion, ⩾2 hospital admissions, ⩾2 surgical procedures or undertaking dialysis. As HCV-related mortality risk is known to be higher in males compared to females and in older persons compared to other age groups [8], the interactions between sex and chronic HCV infection, and between age and chronic HCV infection, on mortality were examined using a likelihood ratio test by adding interaction terms in a Poisson regression model adjusted for other confounders (study village, education and comorbidity). The cohort in Zawiat Razin was used to describe the cause of death, and the association between HCV status and liver-related mortality. Finally, the PAF and its 95% confidence interval (95% CI) were estimated for the effect of chronic HCV infection on all-cause mortality rate (across all three villages) and on liver-related mortality rate (in Zawiat Razin). The "punaf" STATA command was used after fitting a Poisson regression model that included potential confounders and the effect modifiers [29]. All analyses were performed using STATA 13.0 (Stata Corporation, College Station, TX).

Results

Baseline characteristics

A total of 18,111 inhabitants participated in the baseline sero-surveys (4,311 in Aghour El Soughra, 7,385 in Sallam and 6,415 in Zawiat Razin) in 1997–2003. Survey uptake was 62.8%, 75.4% and 77.2%, the prevalence of positive anti-HCV antibodies was 8.7%, 24.3% and 11.8%, and the prevalence of positive HCV RNA in those sero-positive for anti-HCV antibodies was 63.0%, 65.5% and 59.9%, in Sallam [20], Aghour El Soughra [23] and Zawiat Razin [19], respectively.

At the follow-up visit in 2008–2009, vital status was ascertained in 89.9% (16,282) of the initial survey participants. No significant difference was observed in the distribution of HCV status between persons whose vital status was ascertained and persons who were lost to follow-up. The baseline characteristics of these 16,282 participants are presented in Table 1. At the time of enrolment, 1,647 (9.1%) were found to be chronically infected with HCV, 996 (5.5%) to have cleared previous HCV infection and 15,468 (85.4%) had never been infected with HCV (Fig. 1). Compared to those never infected with HCV (n = 13,924), people with chronic HCV infection (n = 1,473) were more likely to be older, of male gender, to have never attended school, and to have comorbidity. Prevalence of chronic HCV infection also differed significantly among the villages: Aghour El Soughra (16.8%), Zawiat Razin (8.2%), and Sallam (5.7%) (p <0.001).

Crude all-cause mortality

During a mean time to follow-up of 8.6 years (139,809 person-years (PY)), 591 (3.6%) died, resulting in an overall mortality rate

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Table 1. Baseline characteristics of 16,282 participants according to HCV infection status.

		Total (n = 16,282)	Chronic HCV infection (n = 1473)	Cleared HCV infection (n = 885)	Never infected (n = 13,924)	*p* value
Median age (years, IQR)		22 (12-36)	40 (30-50)	38 (25-50)	19 (12-32)	<0.001
Sex (n, %)	Female	8326 (51.1)	632 (42.9)	462 (52.2)	7232 (51.9)	<0.001
	Male	7956 (48.9)	841 (57.1)	423 (47.8)	6692 (48.1)	
School	Ever attended	7536 (48.7)	541 (37.6)	312 (36.2)	6683 (50.8)	<0.001
	Never attended	7929 (51.3)	898 (62.4)	549 (63.8)	6482 (49.2)	
Village	Sallam	7127 (43.8)	408 (27.7)	267 (30.2)	6452 (46.3)	<0.001
	Aghour El Soughra	3655 (22.4)	615 (41.8)	358 (40.4)	2682 (19.3)	
	Zawiat Razin	5500 (33.8)	450 (30.5)	260 (29.4)	4790 (34.4)	
Blood transfusion	0-1	16,162 (99.3)	1438 (97.6)	862 (97.4)	13,862 (99.6)	<0.001
	≥2	119 (0.7)	35 (2.4)	23 (2.6)	61 (0.4)	
Hospital admission	0-1	15,361 (94.3)	1339 (90.9)	801 (90.5)	13,221 (95.0)	<0.001
	≥2	920 (5.7)	134 (9.1)	84 (9.5)	702 (5.0)	
Surgical procedure	0-1	15,097 (92.7)	1284 (87.2)	748 (84.5)	13,065 (93.8)	<0.001
	≥2	1184 (7.3)	189 (12.8)	137 (15.5)	858 (6.2)	
Dialysis	No	16,263 (99.9)	1468 (99.7)	882 (99.7)	13,913 (99.9)	0.001
	Yes	18 (0.1)	5 (0.3)	3 (0.3)	10 (0.1)	
Comorbidity[1]	No	14,589 (89.6)	1210 (82.2)	713 (80.6)	12,666 (91.0)	<0.001
	Yes	1693 (10.4)	263 (17.8)	172 (19.4)	1258 (9.0)	

[1]Comorbidity is defined as the presence of any of the following medical history: ⩾2 episodes of blood transfusion, ⩾2 hospital admissions, ⩾2 surgical procedures or dialysis.

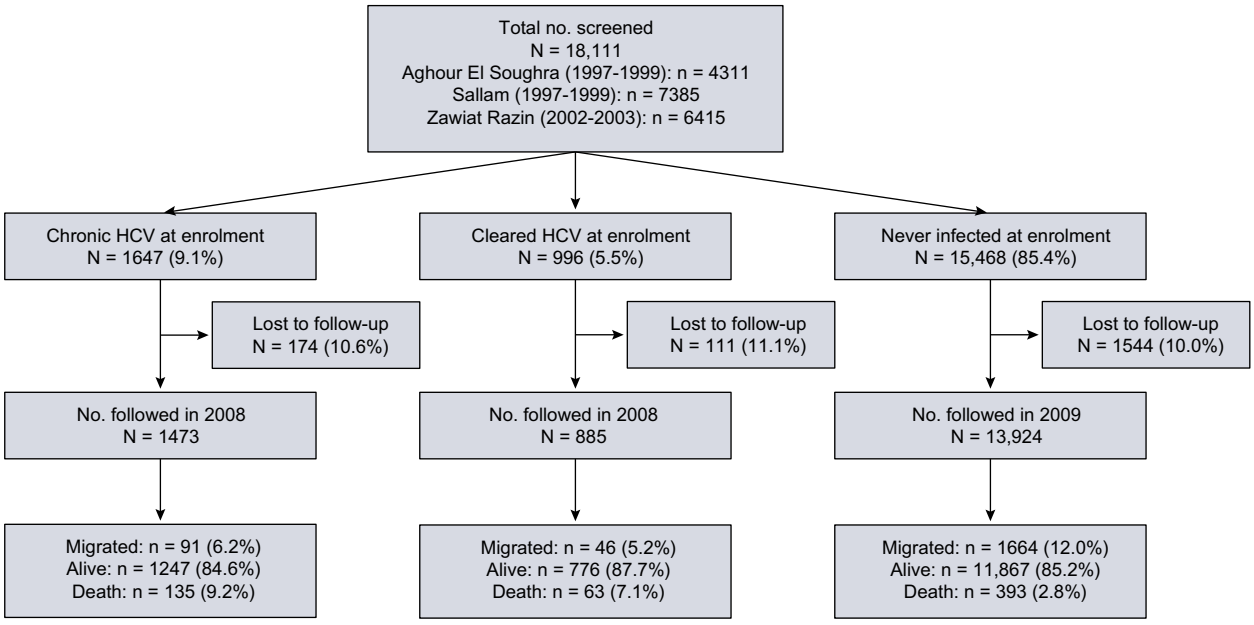

Fig. 1. Flow diagram of study participants.

of 4.2 (95% CI: 3.9–4.6) per 1,000 PY. Across this period, 1,801 (11.1%) participants migrated (Fig. 1). Participants with chronic HCV infection had the highest crude mortality rate (10.4, 95% CI: 8.8–12.3), followed by those with cleared HCV infection (8.0, 6.2–10.2) and those who were never infected with HCV (3.3, 3.0–3.6 per 1,000 PY) (Table 2). However, the higher crude mortality rate observed in subjects with chronic HCV infection may be accounted by their older age and higher male proportion, particularly when compared to the non-infected group. Therefore, only estimates adjusted for confounding factors (among which age and sex) should be considered for meaningful interpretation of the results.

Adjusted all-cause mortality

After adjusting for sex, current age, education, village and comorbidity, the mortality rate of those chronically infected with HCV was significantly higher than that of never infected (MRR: 1.26,

95% CI: 1.02–1.56, $p = 0.03$). There was no difference between those who cleared HCV and those who were never infected (MRR: 0.91, 95% CI: 0.69–1.21, $p = 0.5$). Older age, villages other than Sallam, and the presence of comorbidity were also associated with higher all-cause mortality rate (Table 2).

Age and sex modify the effect of chronic HCV infection on mortality

There was strong evidence that sex modifies the effect of chronic HCV infection on risk of all-cause mortality as compared to those who had never been infected with HCV: the adjusted MRR was 1.55 (95% CI: 1.19–2.02) in men and 0.86 (0.60–1.23) in women ($p = 0.009$, likelihood ratio test). The estimates of the association between chronic HCV infection and all-cause death also found a significant modifying effect of age ($p = 0.008$). Moreover, inclusion of both chronic HCV infection and sex, and then chronic HCV and age groups in the model provided significantly better fit than including either of the interaction terms alone. Consequently, all-cause MRRs comparing patients with chronic HCV infection to those who had never been infected, adjusted for education, village and comorbidity, are presented in ten subgroups stratified by sex and current age groups (Table 3). Among men, the adjusted MRR was 2.35 (95% CI: 1.00–5.49) in those aged <35 years, 2.87 (1.46–5.63) in 35–44 years old, 2.22 (1.29–3.81) in 45–54 years old, 1.45 (0.92–2.27) in 55–64 years old and 1.32 (0.94–1.85) in those aged ⩾65 years. In women, the age-specific MRRs were close to unity across the age groups.

Liver-related mortality

Of the 5,500 people from the village of Zawiat Razin whose vital status was recorded, 155 people died after mean time to follow-up of 6.1 years. Classified cause of death is presented in Table 4. Overall, 13.6% of deaths were liver-related, ranking second after cardiac deaths (18.7%). Among people with chronic HCV infection (n = 30), liver-related death was the most frequent cause (36.7%), followed by cardiac death (10.0%). In contrast, in people who cleared HCV infection (n = 15) and in those who had never been infected (n = 110), cardiac death was the leading cause of death. Compared to people who died from other causes, those who died of liver-related causes had a younger median age (52 years, interquartile range (IQR): 43–61 *vs.* 63, IQR: 49–72, $p = 0.02$) and were more likely to be men (65.0% *vs.* 50.4%, $p = 0.2$).

All-cause and cause-specific MRRs in Zawiat Razin are presented in Table 5. After adjusting for sex, age, education and comorbidity, the strength of association between chronic HCV infection and all-cause mortality in Zawiat Razin (MRR: 1.23) was similar to that observed across all three villages (MRR: 1.26). However, the increase in risk in Zawiat Razin was not statistically significant due to the lack of power with data from one village only: using never infected as a reference, the MRR was 1.02 (95% CI: 0.59–1.77) in those with cleared HCV infection and 1.23 (0.81–1.86) in those with chronic HCV infection. The results were similar in a model that excluded comorbidity as a covariate. In contrast, the incidence of liver-related death was

Table 3. Mortality rate ratios for patients with chronic HCV infection compared to never infected, stratified by age group and sex.

Age group (yr)	Men		Women	
	Adjusted MRR[1]	*p* value	Adjusted MRR[1]	*p* value
<35	2.35 (1.00-5.49)	0.05	1.27 (0.53-3.07)	0.6
35-44	2.87 (1.46-5.63)	0.002	1.55 (0.77-3.13)	0.2
45-54	2.22 (1.29-3.81)	0.004	1.20 (0.67-2.14)	0.5
55-64	1.45 (0.92-2.27)	0.1	0.78 (0.47-1.29)	0.3
≥65	1.32 (0.94-1.85)	0.1	0.72 (0.47-1.10)	0.1

[1]Adjusted for education, village and comorbidity.

Table 2. Factors associated with all-cause mortality.

Variables		PY	No. of deaths	Rate per 1000 PY (95% CI)	Adjusted MRR[1]	
					MRR (95% CI)	*p* value
HCV	Never infected	118,961	393	3.3 (3.0-3.6)	Reference	0.04
	Cleared	7882	63	8.0 (6.2-10.2)	0.9 (0.7-1.2)	
	Chronic infection	12,966	135	10.4 (8.8-12.3)	1.3 (1.0-1.6)	
Sex	Female	70,006	283	4.0 (3.6-4.5)	Reference	0.1
	Male	69,803	308	4.4 (3.9-4.9)	1.2 (1.0-1.4)	
Current age (years)	<15	26,705	12	0.4 (0.3-0.8)	Reference	<0.001[2]
	15-24	40,173	33	0.8 (0.6-1.2)	1.8 (0.9-3.6)	
	25-34	25,954	34	1.3 (0.9-1.8)	2.7 (1.4-5.3)	
	35-44	19,663	48	2.4 (1.8-3.2)	4.9 (2.6-9.3)	
	45-54	13,565	74	5.5 (4.3-6.9)	9.7 (5.2-18.0)	
	55-64	8365	127	15.2 (12.8-18.1)	28.6 (15.7-52.2)	
	≥65	5386	263	48.8 (43.3-55.1)	91.3 (50.7-164.5)	
School	Ever attended	67,964	133	2.0 (1.7-2.3)	Reference	0.2
	Never attended	64,789	428	6.6 (6.0-7.3)	1.2 (0.9-1.5)	
Village	Sallam	68,515	226	3.3 (2.9-3.8)	Reference	0.001
	Aghour El Soughra	37,655	210	5.6 (4.9-6.4)	1.6 (1.3-1.9)	
	Zawiat Razin	33,638	155	4.6 (3.9-5.4)	1.3 (1.0-1.6)	
Comorbidity	No	125,853	471	3.7 (3.4-4.1)	Reference	0.003
	Yes	13,955	120	8.6 (7.2-10.3)	1.4 (1.1-1.7)	

[1]Adjusted for HCV status, sex, current age, education, village and comorbidity; [2]Test for linear trend.

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Table 4. Cause of death by HCV status in Zawiat Razin (n = 155).

	Total (n = 155)	Chronic HCV (n = 30)	Cleared HCV (n = 15)	Never infected (n = 110)
Liver-related	20 (12.9%)	11 (36.7%)	3 (20.0%)	6 (5.4%)
Neoplasms excluding HCC	8 (5.2%)	1 (3.3%)	2 (13.3%)	5 (4.6%)
Stroke	16 (10.3%)	2 (6.7%)	0	14 (12.7%)
Heart disease	30 (19.4%)	3 (10.0%)	4 (26.7%)	23 (20.9%)
Pulmonary disease	7 (4.5%)	1 (3.3%)	3 (20.0%)	3 (2.7%)
Kidney disease	10 (6.4%)	1 (3.3%)	1 (6.7%)	8 (7.2%)
Other	50 (32.3%)	7 (23.3%)	0	43 (39.1%)
Unknown	14 (9.0%)	4 (13.3%)	2 (13.3%)	8 (7.3%)

Table 5. Adjusted cause-specific mortality rate ratios by HCV status in Zawiat Razin (n = 5,500).[1]

Causes	Adjusted MRRs (95% CI)			*p* value
	Never infected (reference)	Cleared HCV	Chronic HCV	
All-cause	1.00	1.02 (0.59-1.77)	1.23 (0.81-1.86)	0.6
Hepatic diseases	1.00	3.83 (0.95-15.47)	7.75 (2.81-21.40)	<0.001
Extrahepatic diseases	1.00	0.77 (0.40-1.48)	0.70 (0.40-1.23)	0.4
Unknown cause	1.00	1.82 (0.37-8.91)	2.04 (0.58-7.20)	0.5

[1]Adjusted for sex, current age, education and comorbidity.

significantly higher among those with cleared HCV infection (adjusted MRR: 3.83 (95% CI: 0.95–15.47)) and those with chronic HCV infection (adjusted MRR: 7.75 (95% CI: 2.81–21.40)). There was no evidence of interaction between HCV status and sex, nor between HCV status and age on hepatic mortality. Non-liver-related mortality rates and death rates with unknown cause did not differ according to HCV status.

Population attributable fractions (PAF)

After fitting a Poisson regression model that included education, village, comorbidity and interactions between HCV infection and sex and between HCV and age, 5.7% (95% CI: 1.0–10.1%) of all-cause mortality rate was attributable to chronic HCV infection. In Zawiat Razin, 45.5% (95% CI: 11.3–66.4%) of liver-related mortality was attributable to chronic HCV infection.

Discussion

This is the first longitudinal community-based cohort study assessing the effect of HCV infection on mortality in a resource-limited setting. In rural Egyptian villages, we found that: i) chronic HCV infection was associated with all-cause mortality in young and middle-aged men, but not in women or older men; ii) chronic HCV infection was a risk factor for hepatic death irrespective of sex and age group; iii) compared to people never infected, those who cleared HCV infection had an increased liver-related mortality rate but similar overall mortality; and iv) 5.7% of all-cause and 45.5% of liver-related mortality rates were attributable to chronic HCV infection.

Similar to previous community-based cohort studies in industrialized countries [12–14,16], we found an increased all-cause mortality rate in people with chronic HCV infection compared to people never infected with HCV. The effect of chronic HCV infection on all-cause mortality differed significantly between sex and between age groups, with this effect of increased mortality only observed in men up to the age of 54 years. Further analysis in the Zawiat Razin cohort suggests that this excess in all-cause deaths was mainly due to an increased liver-related mortality in chronically infected individuals. In this cohort, the median age of liver-related deaths (52 years) was lower compared to that of other causes of death (63 years), implying that in rural Egypt, the relative burden of chronic HCV infection is most important in young and middle-aged men, rather than in older men. One explanation may be that in older men, the increased frequency of cardiac or cerebrovascular events may be diluting the mortality risk associated with chronic HCV infection. There was no increase in mortality rate associated with chronic HCV infection in women when compared to women who had never been infected. It is widely accepted that the speed of progression from asymptomatic chronic HCV infection to liver cirrhosis, and from liver cirrhosis to death is slower in women than men [30–32], which may explain our finding. Still, it is expected that with additional years of follow-up, an increase in HCV-related mortality will emerge in women as well.

In contrast to participants with chronic HCV infection, those who cleared HCV infection had a similar all-cause mortality rate compared to those never infected in this study. This differs from reports from Western countries where injecting drug use is the major mode of HCV transmission and people who cleared HCV share the same lifestyle risks (drug overdose, suicide, murder, excessive alcohol consumption, HIV co-infection) as those who became chronically infected with HCV [8,12,14]. In Denmark, all-cause mortality of people who cleared HCV was significantly higher than that of never infected, except in a subgroup of individuals aged 40–69 years without injecting drug use, alcohol abuse and other comorbidities, implying that in the absence of high-risk behaviours there is little excess mortality in people who cleared HCV infection [14]. However, we found that liver-related mortality was higher in people who cleared HCV infection compared to never infected. This association is not unique to our study and has been observed in previous community-based cohort studies [12,14,16]. This may be explained either by a genuine progression of chronic liver disease despite clearance of the virus in few patients who had advanced fibrosis and who were subsequently treated, or by a misclassification bias, in which the knowledge of anti-HCV positivity may influence the diagnosis associated with the cause of death.

The findings of this study may have been limited by the length of follow-up and potential misclassification of exposure. The risk of advanced liver disease has previously been found to increase 10–20 years after the original infection [33]. If, for example, most of the villagers in these cohorts were infected after 1995, they would not have yet reached the period of elevated HCV-related mortality. Although we do not know the age at which participants were infected, this is an unlikely explanation as it is thought that a substantial number of each cohort were infected much earlier (at least 12.4% of HCV infection in Zawiat Razin in

2002 was attributable to schistosomiasis intravenous treatment programme dated in 1960–1980 [19]). Further, misclassification of HCV status may have occurred as HCV transmission is still ongoing in the villages included in the study, with estimates of 0.1–0.7% of those never infected with HCV at enrolment acquiring HCV infection each year during the study period [22,25]. In addition, 10% of the patients with chronic HCV infection agreed to receive combined PegIFN and ribavirin as part of their participation in the cohort study and, of this group, about half of them achieved sustained viral response (SVR) [27]. The relatively short mean length of follow-and the two possible misclassification errors may mean that the effect of chronic HCV infection on mortality may be slightly underestimated.

In addition, the effect of some HCV transmission risk factors that have been included in previous studies were not assessed in our study: injecting drug use, alcohol abuse, and co-infection with HIV or HBV [13,14,16]. However, these are unlikely to confound the association between HCV infection and mortality in rural Egypt, where injecting drug use, alcohol abuse, and HIV infection are very rare or even non-existent [34,35]. Although HBV is endemic in Egypt (prevalence of chronic HBV infection: 1.7% in general population [36]), and shares the same route of transmission with HCV, its prevalence is similar between people with and without HCV infection in rural Egypt [34].

Overall, the all-cause mortality rate attributable to chronic HCV infection was 5.7% (95% CI: 1.0–10.1%), while liver-related mortality attributable to chronic HCV infection was 45.5% (11.3–66.4%). This has important implications for public health policy and action. In 2006, the Egyptian Ministry of Health and Population established the National HCV Treatment Programme. Since then, more than 200,000 people have been treated with 48 weeks of PegIFN and ribavirin [5]. In 2014, following the agreement between the Egyptian Government and Gilead for the purchase of sofosbuvir at the generic price of $900 (U.S.) for 12 weeks, a new treatment regimen including sofosbuvir was started, and is expected to achieve SVR in >90% of patients [37]. Assuming that SVR rate is 90% with the new regimen and patients who achieved SVR have a similar mortality to people without chronic HCV (i.e., never infected or spontaneously cleared HCV), treating all the villagers with positive HCV RNA may reduce all-cause mortality rate by up to 5% and hepatic mortality rate by up to 40% in rural Egypt, on the basis of the PAFs obtained in our study. Still, due to the huge reservoir of HCV-infected individuals in Egypt, it will take many years until the impact of the National Treatment Programme and other control initiatives on HCV-related mortality can be documented.

In summary, this study described the excess mortality rates associated with HCV infection among young and middle-aged men in high prevalence communities of rural Egypt. This is the first study of this kind to be conducted in a resource-limited setting. These results should be used to inform the prioritisation of patients in the Egypt National Treatment Programme which uses a new highly potent antiviral agent.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Author's contributions

Mostafa K Mohamed, Arnaud Fontanet and Mohamed Abdel-Hamid initiated the cohorts and Arnaud Fontanet, Mostafa K Mohamed and Gamal Esmat were responsible for the design of the current study; Ahmed Medhat, Iman Bakr, and Naglaa Arafa for fieldwork; Mai El-Daly and Mohamed Abdel-Hamid for laboratory assays; and Mostafa El Hoseiny, Nabiel Mikhail, Chesnais Cédric, Aya Mostafa, Yusuke Shimakawa and Arnuad Fontanet for data and statistical analysis. Aya Mostafa and Yusuke Shimakawa drafted the manuscript, and all the authors reviewed and approved it.

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