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Prevalence and Risk Factors of HCV Infection in a Metropolitan Area in Southern Italy: Tail of a Cohort Infected in Past Decades

Filomena Morisco,[1]* Ilaria Loperto,[1] Tommaso Stroffolini,[2] Flavia Lucia Lombardo,[3] Valentina Cossiga,[1] Maria Guarino,[1] Alessia De Feo,[1] and Nicola Caporaso[1]

[1]*Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy*
[2]*Department of Tropical and Infectious Diseases, University of Rome, Rome, Italy*
[3]*National Centre for Epidemiology, Surveillance and Health Promotion, National Institute of Health, Rome, Italy*

Data on the prevalence of HCV infection in Italy are often outdated and from non-urban populations. This study assessed the prevalence and risk factors for HCV infection in a large metropolitan area in southern Italy. A random 1:3 systematic sample of the adult general population of Naples was selected from three general practitioner patient registers in three different city districts. Socioeconomic indicators and risk factors for HCV infection were collected. Anti-HCV and HCV-RNA assays were performed. Logistic regression analysis was used to identify independent predictors of HCV infection. Of 1,500 randomly selected subjects, 1,315 (87.7%) participated in the study. Forty subjects (3.0%; 95%CI: 2.1–4.0) were anti-HCV-positive, with HCV-RNA detected by PCR in 31 (77.5%) of these. Anti-HCV prevalence increased with age, peaking (8.2%) in people born during the years 1945–1955. It was 1.7% in people residing in the better socioeconomic districts; but 5.7% in those residing in the district with lower socioeconomic status ($P < 0.01$). In multivariate analysis, age $\geq$60 years (OR 2.8, 95%CI: 1.3–6.1) and lower educational level (OR 3.6; 95%CI: 1.4–9.3), which is a proxy of low socioeconomic status, were the only independent predictors of the likelihood of anti-HCV positivity. Overall, 22.5% of anti-HCV positive subjects were previously unaware of their status. In the large city of Naples, infection with HCV is most common in people aged older than 60 years. Differences in socioeconomic conditions have played an important role in the spread of this infection. HCV positive subjects born during the years 1945–1955 are those who may benefit, to a greater extent, to be identified in order to receive the new effective therapy. ***J. Med. Virol. 89:291–297, 2017***. © 2016 Wiley Periodicals, Inc.

KEY WORDS: hepatitis C; prevalence; epidemiology; risk factors

INTRODUCTION

Infection with hepatitis C virus (HCV) represents a major global health problem, with the virus estimated to infect approximately 3% of the global population. HCV is the primary cause of chronic liver disease, with the risk of cirrhosis or hepatocellular carcinoma (HCC) of particular concern [Shepard et al., 2005; Grebely and Dore, 2011]. In Italy, several population-based surveys have shown a high prevalence of HCV infection, ranging from 6% to 26% (3–7). Rates have been shown to be particularly high among the elderly (30–42%) with a decreased risk of infection among younger generations, suggesting a cohort effect (i.e., decreased risk of infection along generations). This is attributed to improvements in sanitary and socio-economic conditions. Iatrogenic exposure, in particular past use of non-disposable

Abbreviations: CI, confidence intervals; DAA, direct-acting antiviral; EIA, enzyme immunoassay; GP, general practitioner; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OR, odds ratio; PCR, polymerase chain reaction; PEG IFN-α, pegylated-interferon-α; RNA, ribonucleic acid; SD, standard deviation; SQL, structured query language

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*Correspondence to: Filomena Morisco, Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Naples "Federico II", Via S. Pansini, 5 – 80131 Naples, Italy.
E-mail: filomena.morisco@unina.it

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glass syringes by older generations, has repeatedly been shown to be the major mode of HCV transmission in Italy [Guadagnino et al., 1997; Maio et al., 2000]. A residual role for continuing intra-familial transmission of HCV has also been shown [Guadagnino et al., 1997; Maio et al., 2000].

However, available data on HCV prevalence in Italy present some limitations. Firstly, the results of these studies may be outdated as most were conducted over a decade ago [Stroffolini et al., 1995; Guadagnino et al., 1997; Maio et al., 2000]. A more recent study that was conducted in 2010 as a follow-up of an earlier survey reported an anti-HCV prevalence of 5.7%, a rate much lower than the 12.6% observed 14 years earlier in the same southern Italian town [Guadagnino et al., 1997, 2013]. Other reports have also indicated that the epidemiology of HCV infection has undergone substantial changes over the past two decades, with a progressive decrease in incidence and a shift in risk factors. In addition, many of these earlier studies were conducted in small towns or rural areas, and so may not be representative of the situation in larger urban centers.

A better understanding of the prevalence of HCV is important, especially given the recent advances in its management. Until 2011, the combination of peg-interferon-α (PEG-IFN-α) and ribavirin was the standard of care for treatment of HCV infection. However, the approval of novel direct-acting antiviral (DAA) therapies that offer the potential for cure in nearly all patients have generated a change in the management of HCV infection. DAA therapies offer sustained virological response rates with fewer side effects and their availability has prompted revisions to clinical guideline recommendations. Given this major shift in the treatment of HCV-infected individuals, improved knowledge of the current epidemiology of HCV infection is of considerable interest in helping to inform and resource appropriate therapeutic strategies. Moreover, epidemiological findings need to be validated in different populations in order to better establish the disease burden of HCV infection. Because of this, we performed an epidemiological survey on the prevalence of HCV and risk factors for infection in the general adult population of the metropolitan area of Naples in southern Italy.

PATIENTS AND METHODS

Study Site and Target Population

Naples is the third most populous city in Italy with an estimated 989,111 inhabitants (as of February 28, 2015) and is the biggest urban area in southern Italy. The city is characterized by a population with a diverse socioeconomic status and includes a significant number of multi-ethnic immigrants (3.5% of the population) [Dati ISTAT, 2015]. The mean population density is 8,434 inhabitants/km^2 but this varies greatly among the different residential areas of the city, ranging from 5,000 to 20,000 inhabitants/km^2. The urban area consists of 10 administrative units called districts, numbered from 24 to 34. Each district is characterized by a mean population of 100,000 residents (range 87,000–118,000) [Servizi Statistici del Comune di Napoli, 2010–2012]. The urban space is socially heterogeneous with areas of comparative affluence and well-being and others of social disadvantage.

In order to ensure a study sample representative of the entire urban area, three districts with different socioeconomic characteristics were identified. These were Montecalvario (district no. 31), characterized by low-socioeconomic status, Vomero (district no. 27), characterized by intermediate-socioeconomic status, and Chiaia (district no. 24), characterized by high-socioeconomic status. These three districts were chosen based on the following socioeconomic indicators: population density (persons/km^2: Montecalvario 20,074; Vomero 20,074; Chiaia 9,553), inhabitants with a university degree (Montecalvario 11.5%; Vomero 22.8%; Chiaia: 25.6%), total unemployment rate (Montecalvario 30.2%; Vomero 15.5%; Chiaia 17.1%), home ownership (Montecalvario 49.5%; Vomero 68.3%; Chiaia 58.9%), and number of occupants per room in dwellings (Montecalvario 0.81; Vomero 0.60; Chiaia 0.60) [Servizi Statistici del Comune di Napoli-Censimento, 2011].

A general practitioner (GP) was identified in each of these districts with the intent to conduct a general population based study in adult subjects.

Sampling Procedure

The sample was selected using the three GP's registers, each of which included 1,500 patients, the maximum number allowed by organizational rules of the Italian National Health System. The extraction of subjects from each GP register was done on a random basis, with 500 individuals being selected. Extraction from the .dll library was performed using the following SQL query: "*SELECT cognome, nome, (days-(datanasc, today())/365) AS Eta, sesso, comunasc, indirizzo, comune, cap, provincia, stato_civ FROM V_PAZIENTI WHERE (days(datanasc, today())/365)>18 ORDER BY RAND () LIMIT 500;*."

The GP's registers were last updated through to May 2014. The study was conducted from January to June 2015. Information on the sociodemographic characteristics of subjects and potential risk factors for HCV was collected by a structured precoded questionnaire administered by the GP. The educational level was defined as low (elementary/secondary education only) or high (attended higher education college or university). After informed consent, a blood sample was taken and assessed for biochemical parameters and HCV status assessment.

All study procedures and the questionnaire were reviewed and approved by the Ethical Committee of

the University of Naples, Federico II (Protocol No. 2060/13), and the study was conducted in accordance with the 1975 Declaration of Helsinki.

Laboratory Procedures

Serum samples were separated within 2 hr of collection in two different aliquots. The two aliquots were stored at −30°C until assayed for viral markers. Anti-HCV was checked by a third-generation enzyme immunoassay (EIA) (Ortho HCV 3.0 ELISA; Ortho Diagnostic Systems, Raritan, NJ) according to the manufacturer's instructions. Positive samples were retested in duplicate. In positive cases, the presence of serum HCV-RNA was determined using the Taqman polymerase chain reaction (PCR) assay (Cobas Taqman HCV test, detection limit: 15 IU/ml; Roche Diagnostics, Branchburg, NJ).

Statistical Analysis

Prevalence of HCV was evaluated with 95% confidence intervals (CI). Differences in proportions were tested using Chi-squared and Fisher's exact tests. A P-value <0.05 was considered to be statistically significant. The crude odds ratios (OR), which are estimates of the relative risk linking HCV seropositivity to potential risk factors, were calculated by univariate analysis. Adjusted OR were calculated by multiple logistic regression analysis to identify independent predictors of the likelihood of HCV infection. Only variables that showed a significant association in the univariate analysis were entered into the multivariate model. In the logistic model, anti-HCV positivity was the outcome variable; and age, district of residence, educational level, use of glass syringes, and cohabitation with a HCV positive subject were independent variables. The reference category for OR estimates was that of the most favorable level of exposure. All analyses were performed using STATA, version 13.1 (Stata Corporation LP, College Station, TX).

RESULTS

Among the 1,500 selected subjects, 1,315 (87.7%) agreed to participate in the study (88.2 % in Montecalvario, 87.2% in Vomero, and 87.6% in Chiaia). No differences were detected between participants and refusals according to the district of residence ($P=0.763$). The participation rate was higher in women (90.6%) than in men (83.8%). The mean (±SD) age was not statistically different between participants and non-participants (49.9 ± 5 vs. 47.5 ± 1.4 years; $P=0.07$).

The overall prevalence of anti-HCV was 3.0% (95% CI: 2.1–4.0) (n = 40/1,315). Prevalence was 3.4% (95% CI: 2.0–5.3) in men (n = 17/505) and 2.8% (95%CI: 1.8–4.2) in women (n = 23/810). The prevalence increased from 0.3% in the subgroup of subjects less than 40 years of age to 8.2% in those aged 60–69 years, decreasing to 4.4% in subjects ≥70 years old (Table I).

The overall prevalence was 5.7% (95%CI: 3.7–8.3), 1.4% (95%CI: 0.5–3.0), and 2.0% (95%CI: 0.9–3.8) in the districts with low (Montecalvario), medium (Vomero), and high (Chiaia) socioeconomic indicators, respectively. Because the two districts with medium- and high-socioeconomic conditions did not show statistically significant differences in anti-HCV prevalence, they were combined for subsequent risk factor analyses. Age-specific prevalence by district showed a similar pattern, although rates were higher at all age groups from 40 to 49 years upwards in the district with worse socioeconomic characteristics (Fig. 1).

Risk Factors

The frequencies (%) of demographic characteristics and of the various risk factors reported by anti-HCV-positive and negative subjects are listed in Table II. Anti-HCV-positive subjects were more likely to be older than 60 years (65% vs. 30%; $P<0.001$), resident in the district with lower socioeconomic conditions (63% vs. 33%; $P<0.001$), have a lower educational qualification (33% vs. 74%; $P<0.001$), report use of glass syringes (21.6% vs. 9.9%; $P<0.03$), have received transfusions (5.9% vs. 1.2%; $P<0.02$), and cohabit with an HCV-positive subject (7.5% vs. 2.2%; $P<0.03$). In univariate analysis, crude ORs with 95%CI showed an association between anti-HCV-positive status and age, district of residence, low educational level, use of glass syringes, and cohabitation with an HCV-positive subject. However, after multivariate logistic regression analysis, only age ≥60 years (OR 2.8;

TABLE I. Age-Specific Prevalence of Anti-HCV+, by Gender

	Male		Female		Total	
Age (years)	n	Anti-HCV+ n (%)	n	Anti-HCV+ n (%)	n	Anti-HCV+ n, % (95%CI)
<40	120	0 (0.0)	255	1 (0.4)	375	1, 0.3 (0.0–1.4)
40–49	91	4 (4.4)	177	1 (0.6)	268	5, 1.9 (0.0–4.3)
50–59	107	3 (2.8)	154	5 (3.2)	261	8, 3.1 (1.3–5.9)
60–69	94	6 (6.4)	113	11 (9.7)	207	17, 8.2 (4.8–12.8)
≥70	93	4 (4.3)	111	5 (4.5)	204	9, 4.4 (2.0–8.2)
Total	505	17 (3.4)	810	23 (2.8)	1.315	40, 3.0 (2.2–4.1)

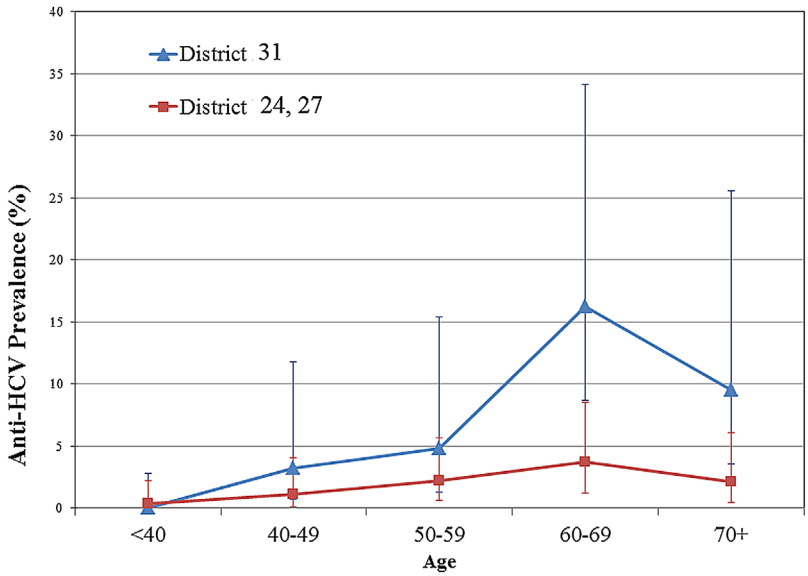

Fig. 1. Age-specific anti-HCV prevalence by district of residence.

95%CI: 1.3–6.1) and low educational qualification (OR 3.6; 95%CI: 1.4–9.3) were independent predictors of being anti-HCV-positive; district of residence, use of glass syringes, and cohabitation with an anti-HCV-positive subject were no longer associated (Table III).

New Diagnosis

Among the 40 anti-HCV-positive subjects who were identified, nine (22.5%) were unaware of their status and so represented a new diagnosis. Among these nine subjects, seven were older than 60 years, eight had low educational qualification, and none had been previously transfused. No differences in distribution of risk factors were observed between these nine persons and the 31 subjects who were already aware of their anti-HCV-positive status.

Characteristics of Anti-HCV-Positive Individuals

The main characteristics of the 40 anti-HCV-positive subjects are detailed in Table IV. Thirty-one (77.5%) were HCV-RNA-positive. Of the nine HCV-RNA-negative subjects, seven had experienced a sustained virological response after a previous IFN-based therapeutic regimen, while the remaining two were likely to have had a spontaneous clearance of the virus. Overall, 11 of the anti-HCV-positive subjects (27.5%) had undergone previous IFN-based treatment.

Three patients showed a cirrhotic status, two of whom were HCV-RNA-positive; one became HCV-RNA-negative after previous treatment with PEG-IFN-α and ribavirin.

Comorbidities were present in 27 of the 40 subjects (67.5%). The most frequent comorbidities were hypertension in 50%, dyslipidemia in 20%, and type II diabetes in 7.5%.

DISCUSSION

The present study is the first survey focusing on a random community-based sample of a general population in a metropolitan southern Italian area. The sampling procedure that was adopted and the high participation rate (87.7%) may have avoided selection and referral biases, generating results that are highly representative of the population being studied. Moreover, the choice of patients from districts with contrasting socioeconomic characteristics may also mean that the population was a good representation of the urban population as a whole.

The observed overall anti-HCV prevalence of 3.0% is lower than that reported in earlier studies [Rapicetta et al., 1992; Stroffolini et al., 1995; Guadagnino et al., 1997; Osella and Misciagna Leone, 1997; Maio et al., 2000]; however, these previous surveys were mostly conducted in the 1990s and the lower prevalence we observed is consistent with the decline in HCV incidence seen in Italy over the past 20 years. Moreover, 3% of the urban population is still a significant number of persons (~30,000 in Naples alone) and represents a substantial health care burden.

The results of multiple logistic regression analysis indicate that both age ≥60 years and lower educational level (i.e., no higher education) are independent predictors of HCV infection. Age is well recognized as a risk factor for HCV infection. In this sample, anti-HCV prevalence increased with increasing age, being highest (8.2%) in people born during the years 1945–1955. This is consistent with other reports that have indicated the highest rates of HCV infection among this generation and confirm that,

TABLE II. Frequencies (%) of Characteristics and Potential Risk Factors Reported by Anti-HCV Positive and Negative Subjects

	Total (N = 1,315)		HCV− (n = 1,275)		HCV+ (n = 40)		
Age	n	%	n	%	n	%	P^*
<60	904	68.8	890	69.8	14	35.0	<0.001
≥60	411	31.2	385	30.2	26	65.0	
Sex							
Female	810	61.6	787	61.7	23	57.5	0.588
Male	505	38.4	488	38.3	17	42.5	
District							
Chiaia-Vomero	875	66.5	860	67.5	15	37.5	<0.001
Montecalvario	440	33.5	415	32.6	25	62.5	
No. of cohabitants							
≤4	1236	94.0	1200	94.1	36	90.0	0.281[c]
>4	79	6.0	75	5.9	4	10.0	
Educational qualification[a]							
Low	356	27.1	329	25.8	27	67.5	<0.001
High	959	72.9	946	74.2	13	32.5	
Glass syringes							
No	1161	89.7	1132	90.1	29	78.4	0.021
Yes	133	10.3	125	9.9	8	21.6	
Transfusions							
No	1281	98.7	1249	98.8	32	94.1	0.017[c]
Yes	17	1.3	15	1.2	2	5.9	
Intravenous drug use							
No	1312	99.8	1272	99.8	40	100	0.759[c]
Yes	3	0.2	3	0.2	0	0	
Cohabitant HCV+							
No	1284	97.6	1247	97.8	37	92.5	0.029[c]
Yes	31	2.4	28	2.2	3	7.5	
Beauty treatments							
No	962	73.2	927	72.7	35	87.5	0.038
Yes	353	26.8	348	27.3	5	12.5	
Heterosexual							
No	3	0.2	3	0.2	0	0.0	0.759[c]
Yes	1312	99.8	1272	99.8	40	100	
Multiple sexual partners							
No	1260	96.0	1221	95.9	39	97.5	0.513[c]
Yes	53	4.0	52	4.1	1	2.5	
Immigrant[b]							
No	1291	98.2	1251	98.1	40	100	0.473[c]
Yes	24	1.8	24	1.9	0	0	

*Chi-squared test.
[a]Low: elementary/secondary school, high: higher education/university degree.
[b]Defined as place of birth not Italy.
[c]Fisher's exact test.

even in a metropolitan area, HCV infection mostly affects the elderly. Age-specific prevalence curves show that the pattern of higher HCV prevalence with increasing age occurred in each district, although this appears to be more marked in the district with poor socio-economic conditions; this may reflect the likelihood that risk factors for HCV infection affected deprived neighborhoods to a greater extent than more affluent communities in previous generations. People currently aged 60–69 years old are thus those who may benefit the most from targeted screening in order to identify HCV infection and receive effective antiviral therapy. Of interest, the prevalence in subjects ≥70 years of age was lower at 4.4% (i.e., approximately half of that seen in those aged 60–69 years). This is likely to be caused by a survival effect, with higher mortality among HCV-infected individuals than non-infected persons in this age group.

Lower educational level, which may be considered an indirect indicator of low socioeconomic status, has been found to be associated with high prevalence of HCV infection in previous cross-sectional studies in the United States [Alter et al., 1994; Armstrong et al., 2002; Denniston et al., 2010], Norway [Dalgard et al., 2003], Denmark [Omland et al., 2013], France [Meffre et al., 2004], Spain [García Comas et al., 2008], Germany [Niederau et al., 2006], Puerto Rico [Pérez et al., 2005], and Pakistan [Maan et al., 2010]. Moreover, a recent US-based study has shown that an educational level of starting college or higher is protective of death for HCV infection as compared to an educational level of less than high school [Ly et al., 2007]. Crude OR estimates showed that residence in the district Montecalvario, which is characterized by a generally lower socioeconomic condition compared to the other two districts included

TABLE III. Crude and Adjusted Odds Ratios (OR) Derived by Multivariate Logistic Regression Analysis

	Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Age		
<60	1	1
≥60	4.3 (2.2–8.3)	2.8 (1.3–6.1)
Sex		
F	1	
M	1.2 (0.6–2.3)	
District		
Chiaia-Vomero	1	1
Montecalvario	3.5 (1.8–6.6)	1.7 (0.7–4.1)
No. of cohabitants		
≤4	1	
>4	1.8 (0.6–5.1)	
Educational qualification		
High	1	1
Low	6.0 (3.0–11.7)	3.6 (1.4–9.3)
Glass syringes		
No	1	1
Yes	2.5 (1.1–5.6)	0.9 (0.4–2.3)
Cohabitant HCV+		
No	1	1
Yes	3.6 (1.1–12.4)	2.4 (0.6–8.5)
Beauty treatments		
No	1	
Yes	0.4 (0.1–1.0)	

NB: by univariate logistic, all variables were associated with the event (anti-HCV positivity) other than sex, number of cohabitants and multiple partners. The multivariate logistic was obtained considering all the significant variables in the univariate logistic, except for beauty treatments as they are of borderline significance.

in this survey, was associated with a higher risk of HCV infection (OR 3.5; 95%CI: 1.8–6.6). However, after adjustment for the confounding effect of all other variables by multiple logistic regression analysis, this variable was no longer associated with increased risk of infection with HCV (OR 1.7; 95%CI: 0.7–4.1). In contrast, lower educational level remained associated with HCV infection in multivariate analysis (OR 3.6; 95%CI: 1.4–9.3). This suggests that residence in the district Montecalvario by itself is a confounding factor, with low educational level the true risk factor.

In our survey, 22.5 % of subjects who were anti-HCV-positive were unaware of their status. These individuals shared the same risk factors as patients who were aware of their infection. In fact, 80% of unaware subjects were older than 60 years of age and 88% had lower educational attainment. This suggests that age >60 years and low educational level may be useful proxies for identifying HCV-positive subjects in the community.

In conclusion, HCV infection in Italy is a disease that primarily affects the elderly, even in a metropolitan area and in cohorts with different socioeconomic backgrounds. Differences in social and economic conditions have played an important role in the past spread of the infection and current prevalence in Italy largely reflects the tail of a cohort infected in previous decades. These factors need to be taken into consideration to help tailor more effective prevention policies and treatment strategies.

TABLE IV. Main Characteristics of Anti-HCV Positive Subjects (n = 40)

Characteristics	Total (n = 40)
Mean age (range), years	63 (39–84)
Sex ratio (male/female)	0.7
HCV-RNA positive	31 (77.5%)
No. of previous IFN-based treatments	11 (27,5%)
Cirrhosis	3 (7.5%)
Coinfection HBV	
HBsAg +	2 (5.0%)
HBcAb + (isolated)[a]	9 (33.3%)
Comorbidity	27 (67.5%)
Hypertension	20 (50.0%)
Diabetes	3 (7.5%)
Dylipidemia	8 (20.0%)
Hypertransaminasemia[b]	34 (85.0%)

[a]Data not available for 13 subjects.
[b]At least one of transaminases >18 UI/ml.

AUTHOR CONTRIBUTIONS

MF and CN participated in the study concept and design; LI, CV, DFA, and GM performed the acquisition of data; LI, ST, and LFL performed the analysis and interpretation of data; MF, LI, and ST participated in the drafting of the manuscript; MF and ST performed critical revision of the manuscript for important intellectual content; LFL and ST performed the statistical analysis; and CN performed the study supervision.

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