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Gender difference in all-cause mortality of people living with HIV in Iran: findings from a 20-year cohort study

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Objectives

Gender differences in the efficacy of treatment and the mortality of HIV-infected patients have not yet been fully elucidated. For the first time, we used data from a 20-year cohort of people living with HIV (PLWH) in four provinces (Fars, Bushehr, Bandar Abbas, and Kohgiluyeh and Boyer-Ahmad) in the southern part of Iran to assess the gender difference in all-cause mortality in PLWH in Iran.

Methods

We analysed data for 1216 patients aged ≥ 15 years who were diagnosed with HIV/AIDS between 1997 and 2017. Three hundred and fourteen (25.8%) were women.

Results

The death rate from all causes among women was 13.7% *vs.* 43.8% among men ($P < 0.001$). All-cause mortality was significantly associated with gender [the adjusted hazard ratio (aHR) for men compared with women was 3.20], not being on antiretroviral therapy (ART) compared with being on ART at the last visit (aHR 5.42), older age (aHR 1.03), delayed HIV diagnosis compared with early diagnosis (aHR 1.72), history of incarceration (aHR 1.57), higher log CD4 count at diagnosis (aHR 0.54), and prophylaxis for *Pneumocystis* pneumonia (aHR 0.09).

Conclusions

Improving early HIV diagnosis and early ART initiation in men, as well as increased access to hepatitis C virus treatment are needed to increase the survival rate of HIV-infected patients in Iran.

Keywords: AIDS, antiretroviral therapy regime, gender, HIV, mortality, survival

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Introduction

Improved access to antiretroviral treatment (ART) has significantly increased the survival rate of people living with HIV (PLWH) [1]. In developed countries, PLWH are living almost as long as the general population [2]; however, in most less-developed countries, the survival rate of PLWH is lower than that of the general population [3]. In previous studies, factors such as a history of drug injection, African American race, and lower CD4 count at diagnosis were associated with higher mortality rates among PLWH [4]. Gender has been reported as a modifier for the risk of HIV infection and its clinical outcomes [5].

According to Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates in 2016, women comprise about half of all HIV-infected people worldwide [6,7]. Gender differences in the efficacy of treatment and the mortality of HIV-infected patients have not yet been fully elucidated. Studies comparing HIV treatment outcomes and mortality between men and women have reported contradictory findings [8–11]. For example, several

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studies have reported a gender difference in the response to ART among PLWH [12–15], while some have suggested a better response to ART only in women [16–18]. However, a few studies have suggested no difference between men and women in the response to ART [19–21]. For example, two studies in Australia [22] and Switzerland [23] reported no significant difference between men and women regarding viral load suppression. Given structural and cultural variation across settings, it is possible that the response to ART in men and women is different in less-developed countries. The observed gender differences in diagnostic delay and treatment adherence [24], HIV viral load at diagnosis [25], and access to treatment services have been suggested as reasons for potential gender differences in HIV treatment outcomes and mortality [26].

In Iran, all HIV diagnostics and treatment services are free. However, use of such services is reported to be very low [27]. According to available estimates, of the 61 000 PLWH estimated to be living in Iran, approximately 22 000 are aware of their HIV status [28]. In 1998, less than 10% of identified Iranian HIV-infected patients were women. In 2018, this number had increased to 33% [29]. In the light of the importance of understanding the factors influencing response to ART, for the first time, we used 20 years of data for a cohort of PLWH in the southern part of Iran to assess the gender difference in all-cause mortality among PLWH in Iran.

Methods

We conducted a 20-year retrospective cohort study among HIV-positive patients who were registered with the Shiraz HIV/AIDS Research Center (SHARC) from August 1997 to May 2017.

Setting

SHARC registers HIV-infected patients in the south of Iran and monitors their clinical status, including treatment and mortality outcomes. At the time of diagnosis, all patients routinely complete a self-administrated questionnaire. The questionnaire includes questions regarding demographic characteristics and risk-associated behaviours. After the first visit, all diagnosed patients follow the ART lines and visit SHARC every 6 months for clinical follow-up. Well-trained staff monitor the patient's treatment status and perform medical tests according to recommendations of the World Health Organization (WHO) [30]. During the 20-year study period, 4810 patients with HIV infection were registered with SHARC; data for 1216 individuals ≥ 15 years of age at the time of diagnosis, and with at least one follow-up visit during the study period, were used for analysis. Patients with no follow-up record and patients < 15 years of age at diagnosis were excluded from the study.

The ethics committee of Shiraz University of Medical Sciences approved the study protocol (ethics code: IR.SUMS.REC.1398.311).

Variables and definitions

Mortality data were collected by linking patients' data to hospital medical records and the registry of deaths. For those who were found to have died by the end of the study period, the survival time (in years) was calculated as the time from the diagnosis of HIV infection to death. For others, the follow-up time was calculated as the time from HIV diagnosis to their last clinical visit. Data on demographic characteristics and risk-associated behaviours were collected at the time of diagnosis. These data included age (continuous), gender (female or male), level of education (below secondary school, secondary school or above secondary school), marital status (married, single or widowed/divorced), occupation (employed or unemployed/housewife), self-reported route of HIV transmission [sexual or injecting drug use (IDU)], history of incarceration (yes or no) and addiction (yes or no). Using patients' medical files, clinical and laboratory data at baseline and during the follow-up visits were collected. Data included ART status (never started or interrupted use vs. using as prescribed), whether the patient was taking prophylaxis for *Pneumocystis carinii* pneumonia (PCP) (yes or no), whether there was a delayed diagnosis [defined as < 1 year between HIV diagnosis and advanced AIDS clinical stage (3 or 4 as defined by WHO)] [31] (yes or no), tuberculosis (TB) coinfection (yes or no), hepatitis C virus (HCV) coinfection (yes or no), and CD4 count. A few patients did not report a route of transmission (n = 18); we added these patients to the other two categories (sexual and IDU) based on their reported history of addiction or risky sexual contact.

Statistical analysis

Median and interquartile range (IQR) for numerical variables (age and CD4 count) are reported. For categorical variables, we report frequency and percentage. The significance of differences between men and women regarding demographic characteristics, risk behaviours and clinical data was assessed using the χ^2 (for categorical

variables) and Mann–Whitney *U* (for numerical variables) tests. Overall survival curves were plotted separately for men and women.

A gender-stratified univariate survival analysis was performed using the Kaplan–Meier method with the log-rank test. A multivariable survival analysis was performed and adjusted hazard ratios (aHRs) with corresponding 95% confidence intervals (CIs) were calculated using a Cox proportional hazard model. The final model was adjusted for gender, age at diagnosis, log CD4 count at diagnosis, PCP prophylaxis, ART status at the last clinical visit, HCV coinfection, addiction history and incarceration history. The multivariable model also included two interaction terms (gender and date of diagnosis, and gender and prophylaxis for PCP). The statistical significance level was set at 0.05. All analyses were conducted in STATA, version 14.0 (Stata Corporation, College Station, TX). Microsoft Excel 2013 (Office 10; Microsoft Corporation, Redmond, WA, USA) was used to make bar and line charts.

RESULTS

We analysed data for 1216 HIV-infected patients, of whom 314 (25.8%) were women (Table 1). The median (Q_1, Q_3) age was 34 (29, 40) years. By the end of the study period, 438 (36.0%) patients had died. The number of deaths from all causes among women and men was 43 (13.7%) and 395 (43.8%), respectively ($P < 0.001$). Compared with men, women had a higher median CD4 count at diagnosis (243 vs. 210 cells/μL for men; $P = 0.003$) and were more likely to be married (53.8% vs. 42% for men; $P < 0.001$), to be unemployed or a housewife (88.2% vs. 40.4% for men; $P < 0.001$), to have been infected via sexual transmission according to self-report (94.9% vs. 11.4% for men; $P < 0.001$), to be on ART (95.2% vs. 74.3% for men; $P < 0.001$), to have received no prophylaxis for PCP (50.6% vs. 40.6% for men; $P = 0.002$), to have had a delayed diagnosis (57.6% vs. 40.3% for men; $P < 0.001$), not to be on TB treatment (97.8% vs. 87.9% for men; $P < 0.001$), and not to be coinfected with HCV (86.3% vs. 16.8% for men; $P < 0.001$).

The test for trend for both genders showed that the trend for mortality rate per 100 person-years (PY) from 1997 to 2016 was significant ($P = 0.006$). The test for trend was significant for men ($P = 0.005$) and women ($P = 0.02$) separately (Figure 1). In men, mortality increased from 0.5 per 100 PY in 2005 to 14.5 per 100 PY in 2014, whereas in women, mortality increased from 0.0 per 100 PY in 2005 to 3.1 per 100 PY in 2013. In 2016, the rates of mortality for men and women were 0.6 and 0.0 per 100 PY, respectively (Figure 1).

The overall 5-year cumulative hazard function (after HIV diagnosis) was 23.4% (95% CI 20.9, 26.0) (Figure 2). The 5-year cumulative hazard function was 12.6% (95% CI 9.1, 17.4%) in women and 26.7% (95% CI 23.8, 29.8%) in men ($P < 0.001$).

As presented in Table 2, the multivariable Cox model showed that being male [hazard ratio (HR) 3.20; $P < 0.001$], being older at diagnosis (aHR 1.03; $P < 0.001$), having a delayed diagnosis (aHR 1.72; $P < 0.001$), not being on ART at the last clinical visit (aHR 5.42; $P < 0.001$) and having an incarceration history (aHR 1.57; P 0.047) were associated with higher rates of all-cause mortality. In contrast, a higher CD4 count at diagnosis (aHR 0.54; $P < 0.001$) and receiving prophylaxis for PCP (aHR 0.09; $P = 0.002$) were associated with lower rates of all-cause mortality.

The strongest risk factors for all-cause mortality among men were older age at diagnosis (aHR 1.03; $P < 0.001$), delayed diagnosis (aHR 1.75; $P < 0.001$), not being on ART at the last clinical visit (aHR 5.40; $P < 0.001$) and having an incarceration history (aHR 1.79; $P = 0.017$). Conversely, a higher CD4 count at diagnosis (aHR 0.63; $P < 0.001$) and prophylaxis for PCP (aHR 0.11; $P = 0.006$) carried a lower risk of all-cause mortality. Among women, not being on ART at the last clinical visit (aHR 4.81; $P < 0.001$) and coinfection with HCV (aHR 3.62; $P < 0.001$) were risk factors for all-cause mortality. A higher CD4 count at diagnosis (aHR 0.09; $P < 0.001$) carried a lower risk of all-cause mortality among women.

There was a significant interaction between prophylaxis for PCP at the last clinical visit and the date of diagnosis.

DISCUSSION

Our research results suggest that, among PLWH, men die at a higher rate than women. Other factors, such as being on ART, HCV coinfection and CD4 count at diagnosis, were also significantly associated with all-cause mortality.

This gender difference in mortality among HIV-positive patients has also been reported in studies from other countries [32]. As reported by Beckham *et al.* [32], among PLWH on ART, men have a significantly greater risk of all-cause mortality compared with women in low- and middle-income countries. Similarly, in another review article, the risk of all-cause mortality among adults was reported to be significantly lower among female patients (HR 0.47) than among male patients (HR 4.90), and the difference was greatest in patients in Gambia [33].

Table 1 Clinical and demographical characteristics of a cohort of 1216 patients living with HIV in southern Iran

Variable	All (n = 1216)	Men (n = 902)	Women (n = 314)	P-value
Deaths from all causes [n (%)]	438 (36.0)	395 (43.8)	43 (13.7)	< 0.001
CD4 count at time of diagnosis (cells/μL) [median (Q_1, Q_3)]	219 (103, 358)	210 (100, 344)	243 (117, 409)	0.003
Age at time of diagnosis (years) [median (Q_1, Q_3)]	34 (29, 40)	34 (29, 40)	34 (29, 40)	0.775
Age at time of diagnosis [n (%)]				
< 30 years	381 (31.3)	280 (31.0)	110 (32.2)	0.933
30–40 years	544 (44.7)	405 (44.9)	139 (44.3)	
> 40 years	224 (291)	217 (24.1)	74 (23.6)	
Marriage status [n (%)]				
Married	548 (45.1)	379 (42.0)	169 (53.8)	< 0.001
Unmarried	668 (54.9)	523 (58.0)	145 (46.2)	
Education [n (%)]				
Less than secondary	422 (34.7)	307 (34.0)	115 (36.6)	0.408
Secondary and above	794 (65.3)	595 (66.0)	199 (63.4)	
Employment [n (%)]				< 0.001
Unemployed/housewife	641 (52.7)	364 (40.4)	277 (88.2)	
Employed	575 (47.3)	538 (59.6)	37 (11.8)	
Route of transmission [n (%)]				
Sexual	401 (33)	103 (11.4)	298 (94.9)	< 0.001
Injecting drug use	815 (67)	799 (88.6)	16 (5.1)	
On ART at last clinical visit [n (%)]				
No or missing	247 (20.3)	232 (25.7)	15 (4.8)	< 0.001
Yes	969 (79.7)	670 (74.3)	299 (95.2)	
Prophylaxis for PCP at last clinical visit [n (%)]				
No	525 (43.2)	366 (40.6)	159 (50.6)	0.002
Yes	691 (56.8)	536 (59.4)	155 (49.4)	
Diagnosis delay [n (%)]				< 0.001
No	671 (55.2)	538 (59.6)	133 (42.4)	
Yes	545 (44.8)	364 (40.4)	181 (57.6)	
Addiction history [n (%)]				
No	317 (26.1)	38 (4.2)	279 (88.9)	< 0.001
Yes	899 (73.9)	864 (95.8)	35 (11.1)	
Incarceration history [n (%)]				
No	404 (33.2)	104 (11.5)	300 (95.5)	< 0.001
Yes	812 (66.8)	798 (88.5)	14 (4.5)	
TB treatment at last clinical visit [n (%)]				
No	1100 (90.5)	793 (87.9)	307 (97.8)	< 0.001
Yes	116 (9.5)	109 (12.1)	7 (2.2)	
HCV infection at last laboratory test [n (%)]				
Yes	794 (65.3)	751 (83.2)	43 (13.7)	< 0.001
No	422 (34.7)	151 (16.8)	271 (86.3)	

ART, antiretroviral therapy; HCV, hepatitis C virus; PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.

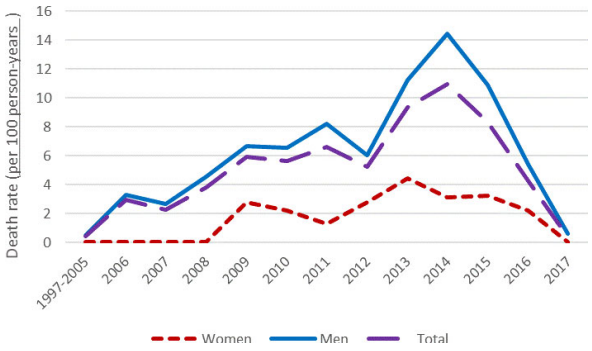

Fig. 1 Trend of mortality rate for all participants, men and women, from 1997 to 2017.

We found that the 5-year survival rate of PLWH after diagnosis was 76.6%. This is similar to that reported by Beckham *et al.*, who found that the survival rate of PLWH receiving ART was 78% [32]. The survival rate of PLWH in our study was better than the rate reported from Zimbabwe (60%) [32,34].

We found that the mortality rate among PLWH had an upward and then a downward trend from 2005 to 2017 for both genders. Briefly, there was an upward trend in mortality rate between 2005 and 2014. However, the mortality rate decreased from 2014 to the end of the study period. A possible reason for the observed downward trend could be a higher ART coverage in Iran after

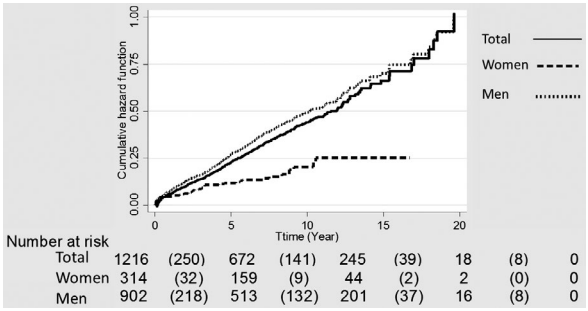

Fig. 2 Cumulative hazard function after HIV diagnosis for all participants, men and women living with HIV in the south of Iran.

2014 [35,36] and efforts such as test and treat in Iran to meet the UNAIDS 90-90-90 goals [7,36].

The observed gender difference in mortality is hypothesized to be attributable to observed differences in the immunological responses to HIV between men and women [18,37]. We found that men had other risk factors for mortality, for example lower ART uptake, a higher prevalence of HCV coinfection (which is a marker for drug injection in the past), and a differential delay in HIV diagnosis. Cornell *et al.* [5] reported gender as an important predictor for 1-year mortality rate even in patients who had the same level of immunological responses to ART. Two other studies from sub-Saharan Africa suggested a better recovery in the immune system in women than in men that increased by longer ART [38,39]. Beckham *et al.* [32] indicated that mortality after ART initiation is significantly higher among men. Some of these effects might be attributable to factors such as delayed diagnosis of HIV infection among men which caused a lower CD4 count and higher viral load and therefore a higher risk of mortality [10,32,40].

We found more women on ART than men. Poorer access to ART in HIV-positive men compared with women was reported in other studies from developing countries [41–43]. Men have been reported to be at higher risk for ART failure than women [44]. However, this finding was not consistent across different countries [23,45]. The reasons for poorer access to ART and treatment uptake among HIV-positive men compared with women could be related to stigma at working place and monthly income of patients [46], discrimination [47], less

Table 2 The all-cause mortality rate and its predictors among a cohort of 1216 patients living with HIV in southern Iran

			All participants		*Men*		*Women*	
Variable	Number of deaths	Death rate (%)	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Gender								
Female	43	13.7	1	< 0.001	-		-	
Male	395	43.8	3.20 (1.22, 4.39)					
Age at diagnosis (for each year increase)	_	_	1.03 (1.02, 1.04)	< 0.001	1.03 (1.01, 1.04)	< 0.001	1.03 (0.99, 1.06)	0.071
Diagnosis delay				< 0.001		< 0.001		0.974
No	265	39.5	1		1		1	
Yes	173	31.7	1.72 (1.39, 2.14)		1.75 (1.40, 2.20)		1.01 (0.46, 2.17)	
Log CD4 count at diagnosis			0.54 (0.43, 0.67)	< 0.001	0.63 (0.50, 0.80)	< 0.001	0.09 (0.04, 0.23)	< 0.001
Prophylaxis for PCP				0.002		0.006		0.358
No	221	42.1	1		1		1	
Yes	217	31.4	0.09 (0.02, 0.42)		0.11 (0.02, 0.54)		0.07 (0.01, 20.66)	
On ART at last clinical visit				< 0.001		< 0.001		< 0.001
Yes	224	90.7	1		1		1	
No	214	22.1	5.42 (4.36, 6.75)		5.40 (4.30, 6.77)		4.81 (2.17, 10.65)	
HCV				0.057		0.768		0.001
No	72	17.1	1		1		1	
Yes	366	46.1	1.39 (0.99, 1.96)		1.05 (0.75, 1.47)		3.62 (1.70, 7.74)	
Addiction history				0.928		0.540		0.261
No	44	13.9	1		1		1	
Yes	394	43.8	1.03 (0.54, 1.93)		0.80 (0.39, 1.63)		1.76 (0.65, 4.74)	
Incarceration history				0.047		0.017		0.646
No	63	15.6	1		1		1	
Yes	375	46.2	1.57 (1.06, 2.47)		1.79 (1.11, 2.90)		0.74 (0.21, 2.58)	
Prophylaxis for PCP × entry time[#]	-	-	1.10 (1.02, 1.19)	0.019	1.09 (1.08, 1.18)	0.043	1.08 (0.80, 1.46)	0.615

ART, antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; PCP, *Pneumocystis carinii* pneumonia.
[#]Positive interaction between prophylaxis for PCP and entry time. Models were adjusted for gender, age at diagnosis, log CD4 count at diagnosis, PCP prophylaxis, ART status at the last clinical visit, HCV coinfection, addiction history and incarceration history.

emotional support from friends and family [48], transportation or financial issues, and work responsibilities [49]. Future studies are needed to understand the personal and social barriers for access to life-saving ART among men.

In our study, delayed diagnosis was found to be one of the main factors associated with higher mortality. Late diagnosis is thus a major issue in the HIV programme in Iran. According to a report, only one-third of Iranian HIV-infected individuals are diagnosed, of whom < 8% receive proper treatment [50]. Although Iran has implemented the "test and treat" strategy since July 2017, the country is nowhere near achieving the UNAIDS 90-90-90 targets [7]. Improving HIV diagnosis and providing patients (particularly men) with care and treatment are the key strategies for improving HIV control in Iran. Early diagnosis of HIV infection is critical, particularly given the clinical benefits of early initiation of ART, which is currently recommended by the WHO [51,52]. There is also a need for more focus on comorbidities, substance abuse and mental health, the known barriers to accessing ART services and adherence to HIV medications among patients [32,53]. As mentioned above, we found that delayed diagnosis was related to an increased chance of mortality. Although women were more likely to have a delayed diagnosis, they had better adherence to ART than men. This may explain why women experienced lower mortality than men [54].

We found that HCV coinfection was associated with higher mortality among women but not among men. Male and female HIV-infected patients with HCV coinfection have delayed CD4 recovery after starting ART and therefore have an increased risk of mortality [55]. Taking a highly effective and tolerable medication for HCV can suppress viral load within 8 weeks of treatment [56]. Thus, the diagnosis and treatment of HCV coinfection among HIV-infected patients is a feasible strategy and should be prioritized. Although HCV coinfection was not significantly associated with mortality among men, incarceration history increased the risk of death by up to 80%. In this study, there is a possibility that the association of HCV and mortality was confounded by incarceration history among men. Supporting our results, Hall *et al.* suggested that incarceration history significantly increases the risk of mortality among HIV-infected individuals [57].

After controlling for other potential confounders, including incarceration history and delayed diagnosis, we found that addiction had no significant impact on mortality in men or women. This finding is in line with a few previous reports from Iran [58] and other countries [59]. However, another study reported otherwise [60].

Finally, it should be noted that AIDS- and non-AIDS-related mortality rates using data from this 20-year cohort study have been presented previously [61].

Although the findings of this 20-year cohort study offer new insights, our study had some limitations. First, as a consequence of the high rate of loss to follow-up of patients and some cultural issues, underreporting and low quality of the data were inevitable. To tackle this issue, we checked and completed the data as much as possible, bearing in mind that loss to follow-up is a common issue in cohort studies with such a long period of follow-up [62]. Moreover, as the transmission routes were self-reported in our study, there may have been information biase in the data. However, it is possible that this was only a minor issue, as the two main routes of transmission found (i.e. IDU and heterosexual contact) are considered the main HIV transmission routes in Iran [61,63]. We used the existing data that were collected at the time of diagnosis and during the clinical follow-up visits with missing data. For example, data on viral load were not collected before 2011. Also, the iceberg phenomenon for HIV/AIDS in Iran should be taken into account, as the majority of infected individuals are likely not to be diagnosed as a result of stigma and other barriers [64]. Obviously, we could only measure mortality among HIV-infected patients who had been diagnosed. So, the generalizability of our results to all PLWH in Iran, especially those who have not been diagnosed, should be taken into consideration when interpreting the results. Finally, we may have missed the death outcome in some of our study subjects if the death was not registered or the name of the patient that was used to link the data was missing or inaccurate.

Conclusions

The results of this study suggest that gender is an important predictor of survival among HIV-infected patients. CD4 count at diagnosis, age, delayed diagnosis and HCV/HIV coinfection were highly associated with the mortality of the patients. The findings demonstrate that early initiation of ART and treatment of coinfections can improve the survival rate in both genders.

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Availability of data and material: Data and material are available upon request.

Author contributions

ZG and MD contributed to the design and implementation of the study and the analysis and interpretation of the data, and were involved in drafting the manuscript. AH and AM contributed to the interpretation of results, and drafting and revising the manuscript. MF and ZG contributed to the conceptualization and design of the study and drafting of the manuscript. All authors reviewed and approved the final version for publication.

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