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Trends in Mortality and Causes of Death among Women with HIV in the US: A Ten-year Study

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Abstract

Background—To assess trends in mortality and cause of death for women with HIV, we studied deaths over a 10 year period among participants in the Women's Interagency HIV Study (WIHS), a representative US cohort.

Methods—Deaths were ascertained by National Death Index-Plus match and causes of death determined by death certificate.

Results—From 1995 through 2004, 710 of 2792 HIV-infected participants died. During this interval the standardized mortality ratio (SMR) fell from a high of 24.7 in 1996 to a plateau with a mean of 10.3 from 2001–2004. Over the decade, deaths from non-AIDS causes increased and accounted for the majority of deaths by 2001–2004. The most common non-AIDS causes of death were trauma or overdose, liver disease, cardiovascular disease and malignancy. Independent predictors of mortality besides HIV-associated variables were depressive symptoms, and active hepatitis B or C. Women who were overweight or obese were significantly less likely to die of AIDS than women of normal weight.

Conclusion—In the WIHS, the death rate has plateaued in recent years. While HIV-associated factors predicted AIDS and non-AIDS deaths, other treatable conditions predicted mortality. Further gains in reducing mortality among HIV-infected women may require broader access to therapies for depression, viral hepatitis and HIV itself.

Keywords

HIV; mortality; women; viral hepatitis; non-AIDS mortality

Introduction

With the advent of potent antiretroviral therapy in the mid-1990's, the rate of HIV-related death in the United States declined dramatically and has continued to decline (1,2). However, women with HIV did not experience the same magnitude of decline in death rate with the original introduction of highly active antiretroviral therapy (HAART) and have experienced a lesser subsequent decline in mortality compared to men with HIV (3,4). Women of color with HIV have particularly high death rates in the HAART era compared to other groups (5). In light of these epidemiologic data, we sought to understand causes of death and factors that precede death among women with HIV, including those that may influence non-AIDS mortality. We studied the temporal trends, causes and predictors of mortality in a representative US cohort, the Women's Interagency HIV Study (WIHS), over a ten-year period from 1995 through 2004.

Methods

The WIHS is a longitudinal study of HIV-infected and demographically similar HIV-uninfected women that enrolled 2054 HIV-infected women and 569 uninfected women at six locations, Chicago, San Francisco Bay Area, Brooklyn and Bronx/Manhattan, New York, Washington, DC and Los Angeles from October 1994 through November 1995. An additional 738 HIV-infected women and 406 uninfected women were enrolled from October 2001 through September 2002 to increase the number of young women in the cohort. This study will involve data from only the HIV-infected women because the number of deaths among HIV uninfected women was too small to evaluate trends and predictors. Informed consent was obtained from all participants in accordance with the US Department of Health and Human Services guidelines and the institutional review boards of participating institutions. Women were seen semiannually for an interview, physical exam and collection of blood and genital specimens. The cohort was designed to reflect the demographics of the HIV epidemic among women in the United States. Details of cohort recruitment, retention and demographics have been previously published (6,7).

Ascertainment of deaths

In order to detect all deaths among WIHS participants, a number of active and passive ascertainment methods were employed. Death certificates were obtained from medical records and local health departments as soon as the study staff became aware of a death. To assure that all deaths in the US were ascertained, National Death Index (NDI)-Plus searches were performed annually for all WIHS participants who were known to have died or were lost to study follow-up. The NDI-Plus provides information on deaths that occur throughout the US and US territories and provides all the primary and underlying causes from the original death certificates. All death certificate data were reviewed independently by two clinicians using specific criteria which classified a death as AIDS-related if an AIDS-defining infection or malignancy was the cause of death or if the cause of death was pneumonia or sepsis in the setting of a recent CD4 count <200 cells/mm³. Deaths were classified as indeterminate if the cause of death was entirely non-specific (most frequently "cardio-pulmonary arrest"), if the death certificate had conflicting causes or had HIV as the only cause of death for a woman whose CD4 count was ≥ 200 cells/mm³ at the most recent WIHS visit. Deaths were classified as non-AIDS if a non-AIDS cause was the primary cause of death.

Statistical Methods

To control for age, standardized mortality ratios for HIV-infected women were calculated for each calendar year using the National Center for Health Statistics Compressed Mortality File data for US females (8). The standardized mortality ratio (SMR) divides the observed number of deaths by the expected number of deaths using the age-specific rate from a standard

population (9). Mortality rates (number of deaths per 100 person-years of follow-up) were also calculated for AIDS and non-AIDS causes of death. Proportionate mortality was presented by two year increments.

Univariate and multivariate multiplicative hazard models were used to evaluate the associations between death and several factors. The multiplicative hazard models calculated hazard ratios (HR) and their 95% confidence intervals (CI) to determine which factors were associated with death from all causes, AIDS-related deaths, non-AIDS deaths and specific causes of non-AIDS deaths. Deaths that were classified as unknown or indeterminate were included only in analyses of all-cause death.

For the multiplicative hazard models, multiple records were created for each subject, one record for each distinct pattern of the time-dependent and fixed measurements, thus creating several unique risk intervals per subject. Each record contained a time 1 (t1) value and a t2 value representing the risk interval (t1,t2) during which the values of the explanatory variables remained unchanged. Each record also contained the censoring status at t2. Each woman contributed time at risk from the date of enrollment until death, or the last date seen alive.

Several fixed effects and time-dependent variables were initially explored as potential predictors of death. Fixed effects included race/ethnicity, age at baseline, hepatitis B surface antigen (HBsAg) status, composite hepatitis C virus (HCV) status (anti-HCV negative, anti-HCV positive/HCV RNA negative or anti-HCV positive/ RNA positive) and cohort (1994–95 recruitment or 2001–2 recruitment). Time-dependent variables were measured at each visit and included HIV viral load (log transformed), CD4+ T lymphocyte cell (CD4) category (<200, 200–350, >350 cells/mm³), history of AIDS-defining illness, smoking status, injection drug use, heavy alcohol consumption (>14 drinks/week), crack, cocaine or heroin use (as a composite variable), body mass index (BMI, weight in kg/ height in meters²), income (≥ or < \$18,000/ year), Center for Epidemiologic Studies-Depression Scale (CES-D) score (<16 not depressed, ≥16 depressed), recent domestic violence and HAART use defined by the contemporary Department of Health and Human Services Guidelines (10). All variables except race/ethnicity and domestic violence were found to be associated with mortality in the univariate model. We found, in preliminary analyses, that history of injection drug use was collinear with hepatitis C antibody status; we chose to retain hepatitis C status and the composite drug use variable (which includes injection and non-injection drug use) in the final models. In preliminary models, age and HIV-associated variables accounted for the differences in survival rates for the era of recruitment, therefore the cohort variable was eliminated from the final model. Therefore the final model included all of the hypothesized variables except injection drug use, domestic violence and era of recruitment. Race, though not significantly associated with mortality in the univariate model, was retained in the final model as a variable of interest. Several variables that have been known to increase survival in HIV, including opportunistic infection prophylaxis and number of primary care visits, were not included in the model because the data were either not collected throughout the entire WIHS or the methods for collection changed substantively during the study.

Results

From 1995 to the end of 2004, 710 HIV-infected WIHS participants died. Baseline demographic and disease characteristics are presented in Table 1. The yearly SMRs for WIHS decedents over the 10 years of the study are presented in Figure 1 (not included are four HIV-infected decedents for whom the year of death is unknown). There has been a substantial decline in the SMR for WIHS women since the mid-1990s, however the decline has not continued and the SMR reached a plateau with a mean of 10.3 from 2001 to 2004 compared to the age-adjusted US female population. Using simple death rates, the trend was similar, with a substantial

decrease from 8.0 per 100 person-years in 1996 down to a plateau with a mean of 2.6 per 100 person years in 2001 through 2004.

Trends in Causes of Death

Figure 2 demonstrates the causes of death for HIV-infected decedents from 1995 through 2004 (the 4 deaths without known date are not included). During the early part of the study, as expected, AIDS deaths predominated. In the later years, AIDS still accounted for approximately half of the deaths but non-AIDS deaths increased as a proportion of deaths. The total number of non-AIDS deaths per year increased slightly in the HAART era but the increase was not significant. The major causes of non-AIDS deaths were liver-related (42), cardiovascular mortality (33), non-AIDS malignancies (31) and accidental, self-induced or violent deaths (55). Miscellaneous causes of non-AIDS deaths included renal (12), neurologic (11), gastrointestinal (10), infections (5), pulmonary (4), complications of surgery or childbirth (4) and other causes (10) with no discernable trends over time.

While AIDS deaths decreased over time, they still accounted for 53% of deaths from 1998 to 2004, an era during which potent ART was widely available. Of 183 WIHS participants who died of AIDS during 1998–2004, 165 had a visit in the 14 months prior to death. Of those 165, 61 (37%) were on HAART during at least one visit prior to death. Of the 61 women on HAART, only four had undetectable plasma HIV RNA during a WIHS visit in the 14 months prior to death. In fact, these 61 women had non-suppression for 217/239 (90%) of WIHS visits where they reported HAART. Non-adherence to antiretroviral regimens may account for some but not all of the lack of viral response; of 80 visits during the year before death with adherence data, adherence of least 95% was reported for 57 (71%) of the visits where HAART was reported. The majority of these women started antiretroviral therapy with a regimen that was not considered HAART.

No death certificate information was available for 20/710 (2.8%) of deaths. Death certificates were indeterminate, i.e. lacked adequate information to determine cause, in 54/710 (7.6%) deaths. The majority of indeterminate deaths (29) had death certificates with “HIV infection” as the only cause of death in women who had a recent WIHS CD4 count ≥ 200 cells/mm³, 21 had conflicting or uninterpretable causes of death and four certificates listed “cardiopulmonary arrest” as the only cause of death.

Predictors of mortality

We analyzed predictors of all-cause mortality, AIDS-related and non-AIDS death among HIV infected women (Table 1). As expected, HIV-associated characteristics including CD4 count and plasma HIV RNA level were potent predictors of mortality, with HIV RNA predicting non-AIDS as well as AIDS deaths. Low BMI and HBsAg positivity were also predictive across analyses. Hepatitis C status predicted all-cause and non-AIDS mortality. A predictor of particular note was depressive symptoms, as defined by CES-D score ≥ 16 , which was predictive of all categories of mortality. High BMI was negatively associated with AIDS death compared to women of normal weight.

In order to understand why the death rate among HIV-infected women has not continued to decline after introduction of potent antiretroviral regimens, we examined the predictors of mortality assessed in Table 1 for 2001–2004, during which HAART was widely used among WIHS participants, and compared these to predictors in the pre- and early HAART era (1995–97). We chose 2001 to 2004 because the age-adjusted death rate and SMR had clearly plateaued among HIV-infected WIHS women through that period. Predictors of all cause mortality were much the same in both eras (data not shown). CD4 cell depletion to <200 cells/mm³ (HR 6.02 (3.86–9.40), 1995–97 and 4.38 (2.74–6.99), 2001–4) and HIV RNA level (HR 1.69 (1.44–

1.99), 1995–97 and 1.29 (1.10–1.53) 2001–4) remained important predictors of mortality in both time periods although with reduced hazard ratios in the recent era. Depressive symptoms, older age, and BMI <18.5 were significant predictors for overall mortality in both eras with non-significant increases in hazard ratios in the recent era. Hepatitis C viremia was not a significant predictor in the early HAART era but became predictive for 2001–4 (HR 1.78 (1.15–3.12) 2001–4).

We analyzed the potential predictors listed in Table 1 for the major causes of non-AIDS mortality, including liver, cardiovascular, non-AIDS malignancies and self-induced/traumatic death. Table 2 summarizes the significant predictors with CD4 count included as a predictor of interest. CES-D ≥ 16 was again an important predictor, especially for cardiovascular deaths and non-AIDS malignancies. Liver deaths, as expected, were associated with HCV viremia and the presence of hepatitis B surface antigen in serum.

Discussion

In this ten year study of mortality trends among HIV-infected US women we found that the death rate has plateaued after a substantial decrease during the early HAART era, despite the addition of younger, healthier women to the cohort in 2001–2. Mortality from non-AIDS causes has become increasingly common; with the major causes of non-HIV related death being violence or self-harm, non-HIV associated cancers, cardiac and liver disease. While these findings are largely consistent with those of other recent cause of death studies among HIV-infected persons, we identified several trends and predictors that suggest interventions that may reduce morbidity and mortality among HIV-infected US women.

Despite the increasing role of non-AIDS deaths, women with HIV in the WIHS continue to die of AIDS; 53% of deaths with known cause from 1998 to 2004 were due to AIDS. Several other large cohorts have reported a smaller proportion of deaths due to AIDS in the HAART era than that observed in the WIHS (11–13) though differences in the definition of AIDS death must be taken into account. For example, in the multicenter CASCADE collaboration, AIDS death accounted for only 37% of deaths with known cause from 1998 to 2003 among 7680 HIV-infected individuals (12). In the D:A:D study, among 23,441 HIV-infected persons from December 1999 through February 2004, 31% of deaths were due to AIDS although the definition of AIDS death was restrictive. (13). In contrast, the US HIV Outpatient Study found that 61% of deaths with known cause from 1998–2004 were due to AIDS, although, again, the definition of AIDS death differed slightly from ours (14). In our study, HIV-related characteristics continue to be predictive of all-cause mortality, even in the present era. Several large epidemiologic studies have shown that female sex is associated with increased morbidity and mortality among HIV-infected persons (15–17) and CDC mortality data reveal that since the widespread availability of potent treatments, women with HIV have not enjoyed the same magnitude of decline in mortality as men (3). It is also clear that women have not used HAART at rates equivalent to those of men since the beginning of the HAART era (18,19). In our study, of 165 women who died of AIDS during 1998–2004, only 61 were on HAART at any visit in the 14 months prior to death. The majority of these women reported adherence but had detectable HIV RNA for 90% of the visits prior to death. In a cross-sectional study in the WIHS in 2000–2001, we demonstrated that among 889 women with medical indications for HAART, 29% were not using it; recreational drug use, history of physical or sexual abuse and non-white race were associated with non-use of HAART (20).

The most common cause of non-AIDS death in our cohort was trauma and intentional or unintentional self-harm, most commonly overdose. This rate exceeds that reported in many cohorts (11,21) though it is similar to cohorts of HIV-infected injection drug users and HIV-infected persons in Southern Alberta where the prevalence of drug abuse among HIV-infected

persons is high (15,22). Factors in the WIHS that may contribute to this high rate of violent death and suicides are the prevalence of depressive symptoms, the high rates of physical abuse suffered by WIHS women (23) and the ongoing vulnerability associated with poverty and substance abuse. There may be physiologic reasons for this high rate as well; HIV-infected drug users in the AIDS Link to Intravenous Experience (ALIVE) study were more than twice as likely to die of overdose than HIV-uninfected drug users. The authors of this report postulated that a portion of this discrepancy was due to medical conditions and abnormal liver function in the HIV-infected drug users (24). We found an unexpected relationship between HIV RNA level and overdose/traumatic death. Of interest, the Strategies for the Management of Antiretroviral Therapy (SMART) study reported a relationship between overdose and deferred antiretroviral therapy (25). Rates of accidental or injury related mortality in the WIHS were specifically compared to rates for men in the Multicenter AIDS Cohort Study (MACS) by Hessol et al. Women participating in the WIHS had significantly higher death rates from injury and accident than men in the MACS and, in multivariate comparisons traumatic deaths were associated with female sex, injection drug use, depressive symptoms, unemployment, and smoking (21).

One striking finding of our analysis was the consistency of the predictive role of depressive symptoms on mortality among HIV-infected women. CES-D ≥ 16 was an independent predictor of AIDS and non-AIDS related mortality throughout the decade of study observation. Depression is generally more common among women than men and highly prevalent in the WIHS, with 31% of women chronically reporting depressive symptoms and an additional 37% with intermittent depressive symptoms (26,27). The association of depression with AIDS-related death was described previously by the WIHS and other studies (27,28) although has not been consistently found by all investigators (29). We originally postulated that this association was mediated through nonuse of potent antiretroviral therapy among depressed persons, however, we found the association was independent of HAART use. Furthermore, depressive symptoms were associated with the four most common causes of non-AIDS mortality affecting these women; these associations were statistically significant for cardiovascular disease and non-AIDS malignancies (Table 2).

A notable finding was the negative association between high BMI and AIDS death. Overweight and obesity are very common in the WIHS, with 54.2% of women overweight (BMI ≥ 25) including 25.7% obese (BMI ≥ 30) at WIHS baseline. Compared to women with normal BMI, women who were overweight had a significantly lower hazard ratio of AIDS deaths and the hazard was smaller as BMI increased, 0.63 (95% CI 0.45–0.89) for overweight women non-obese women and 0.48 (0.31–0.73) for obese women. This association has been found in mixed-gender cohorts and smaller cohorts of HIV-infected women (30,31). Others have found that obesity affects T-cell subset frequency and may be associated with higher CD4+ T-lymphocyte counts in HIV-infected and uninfected persons (32–34).

There has been much interest in the role of viral hepatitis in HIV disease progression and mortality and several studies have reported that liver disease is the most common cause of non-AIDS death among HIV-infected persons (11,13). Liver-related deaths were the second most common cause of non-AIDS death in our cohort. Liver-related deaths were associated with viral hepatitis, as expected. Although there was a trend toward a predictive role for low CD4 count, we did not find the significant association of markers of immune dysfunction and liver deaths that has been found in other studies. In the large D:A:D and CASCADE studies, low CD4 counts strongly predicted liver-related mortality (13,35). In contrast to some investigators, we did not find that viral hepatitis was predictive of AIDS death (36).

Limitations

Causes of death, in our study, were ascertained by death certificate. While this is the method used in the vast majority of published mortality analyses, the limitations of death certificate data are well known and may be a particular problem in HIV/AIDS (37–39). We have attempted to increase the accuracy of cause of death classification using other data available in the WIHS. Because we used consistent and thorough methodology for ascertaining cause of death and a well-defined algorithm to classify deaths consistently over time, we believe that the trends we identified are robust. The use of CD4 count as part of the definition of AIDS death, we believe, increases the accuracy of certain categories of death but it precludes the use of CD4 as a predictor of AIDS death and complicates the evaluation of the relationship between CD4 and non-AIDS deaths.

While the CES-D has been found to be sensitive tool in a variety of populations and is widely used and validated in HIV-infected persons (40–42), it contains several questions that could reflect physical debility rather than depression. Thus there is the potential that the CESD may over-estimate depression in some women.

Conclusions

In this cohort of HIV-infected US women, mortality declined dramatically with the introduction of HAART. However mortality has not continued to decline, but has plateaued over the last several years at a rate 10 times greater than age-matched US women. We found that HIV-related factors were the most potent predictors of mortality, but a number of treatable conditions, most notably depression and viral hepatitis, were also associated with mortality across time and analyses. Further gains in reducing mortality among HIV-infected women may require broader access to available therapies for depression, viral hepatitis and HIV itself.

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Figure 1.
Standardized mortality ratios for HIV-infected women 1995–2004 (standardized to CDC
Compressed Mortality File for US females (8))

Figure 2.
Causes of Death for HIV-infected WIHS participants, 1995–2004

Table 1

Baseline Cohort Characteristics and Predictors of Death among HIV-infected women: Multiplicative Hazard Model

Predictors	Descriptive Characteristics of Cohort at Baseline* N=2792 % (n)	Overall Mortality N=710 HR (95% CI)	AIDS Deaths N=418 HR (95% CI)	Non-AIDS Deaths N=218 HR (95% CI)
Baseline variables				
Age	Mean 35.96 (sd 7.86)	1.03 (1.02–1.04)	1.02 (1.00–1.04)	1.05 (1.02–1.07)
Race				
Non-Hispanic Black	58.0 (1618)	0.93 (0.73–1.2)	0.95 (0.68–1.34)	0.98 (0.63–1.51)
Non-Hispanic White	23.2 (649)	Ref	-	-
Hispanic	15.6 (435)	0.81 (0.59–1.11)	0.96 (0.63–1.47)	0.95 (0.55–1.65)
Other	3.2 (90)	0.68 (0.34–1.36)	0.64 (0.27–1.52)	0.24 (0.03–1.80)
HBsAg				
Positive	2.8 (78)	1.95 (1.30–2.92)	2.09 (1.22)	2.41 (1.16–4.97)
Negative	95.2 (2657)	Ref	-	-
Unknown	2.0 (54)			
HCV status				
Anti-HCV –	62.9 (1755)	Ref	-	-
Anti-HCV+/RNA–	5.9 (164)	1.30 (0.87–1.93)	0.94 (0.52–1.82)	1.98 (1.11–3.55)
Anti-HCV+/RNA+	25.8 (719)	1.36 (1.09–1.70)	0.94 (0.69–1.29)	2.11 (1.42–3.55)
Unknown	5.5 (154/2792)			
Time-varying variables [‡]				
CD4 count				
>350	53.4 (1491)	Ref	†	-
200–350	22.2 (619)	1.43 (1.03–1.98)		1.33 (0.89–1.50)
<200	24.4 (682)	4.40 (3.35–5.79)		1.39 (0.92–2.10)
Mean Log Viral load	4.01 (sd1.163)	1.53 (1.38–1.69)	3.26 (2.82–3.78)	1.28 (1.09–1.50)
History of AIDS				
defining illness	5.8 (163)	1.33 (0.94–1.89)	3.80 (1.68–8.61)	0.83 (0.53–1.29)
HAART use				
Yes	12.5 (349)	0.84 (0.65–1.08)	0.95 (0.63–1.43)	0.81 (0.55–1.21)
No	87.4 (2440)	Ref	-	-
Crack, cocaine or heroin				
Ever	59.4 (1656)	1.02 (0.78–1.34)	0.90 (0.64–1.28)	1.53 (0.87–2.68)
Never	40.4 (1129)	Ref	-	-
Smoking				
Ever	67.4 (1881)	0.99 (0.75–1.31)	0.86 (0.61–1.23)	1.35 (0.77–2.38)
Never	32.2 (900)	Ref	-	-
Heavy drinking				
Current	7.3 (204)	0.88 (0.60–1.29)	0.71(0.40–1.24)	0.89 (0.47–1.69)
Ever	16.2 (452)	1.05 (0.84–1.33)	0.90 (0.64–1.28)	1.12 (0.78–1.60)
Never	76.5 (2136)	Ref	-	-
CES-D≥16	52.9 (1476)	1.60 (1.32–1.92)	1.41 (1.08–1.83)	2.03(1.44–4.97)
Income ≤\$18,000/year	71.1 (1985)	1.18 (0.92–1.515)	0.95 (0.69–1.32)	1.54 (0.96–2.46)
Unstable housing	11.0 (306)	0.84 (0.61–1.17)	0.87 (0.56–1.38)	0.74(0.42–1.29)
Body mass index				
<18.5	3.2 (89)	2.74 (2.11–3.56)	3.28 (2.35–4.59)	2.85 (1.72–4.71)
18.5–25	38.4 (1071)	Ref	-	-
≥25–30	28.5 (796)	0.72 (0.56–0.92)	0.63 (0.45–0.89)	0.84 (0.55–1.28)
≥30	25.7 (717)	0.82 (0.63–1.06)	0.48 (0.31–0.73)	1.19 (0.80–1.78)
Unknown	4.3 (119)			

Note- abbreviations: HR: Hazard Ratio, CI: confidence interval, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, HAART: highly active antiretroviral therapy, CES-D : Center for Epidemiologic Studies-Depression scale, Values in bold are statistically significant, p<0.05

* Several variables have missing data, the number of women with missing data is not shown if the missing data comprise less than 1% of the total, therefore some cells show fewer than 2792 women

[†] Values in the first column are baseline variables to give the reader a sense of cohort characteristics at baseline, all analyses were done using time-varying data

[‡] Because CD4 count is used to categorize AIDS deaths, CD4 was not included in the model for AIDS deaths

Table 2

Predictors of non-AIDS death among women with HIV

	Liver HR (95% CI)	Cardiovascular HR (95% CI)	Non-AIDS malignancies HR (95% CI)	Overdose/trauma HR (95% CI)
Age (per year increase)	1.04 (0.99–1.09)	1.10 (1.04–1.16)	1.08 (1.01–1.15)	1.01 (0.96–1.06)
CD4 <200	2.09 (0.91–4.81)	1.75 (0.59–5.20)	2.08 (0.41–10.58)	0.96 (0.45–2.05)
Log 10 HIV-RNA (per log increase)	1.25 (0.90–1.72)	1.00 (0.68–1.49)	1.45 (0.91–2.30)	1.52 (1.11–2.10)
HCV RNA+	9.51 (3.19–28.37)	0.83 (0.31–2.18)	1.52 (0.50–6.93)	1.78 (0.84–3.76)
HBsAg+	5.47 (1.57–19.04)	2.25 (0.29–17.48)	2.07 (0.25–17.15)	0.77 (0.10–5.82)
CES-D >16	1.68 (0.80–19.04)	4.61 (1.55–13.74)	3.01 (1.06–8.53)	1.92 (0.98–3.75)
BMI <18.5	6.31 (2.37–16.81)	3.66 (1.10–12.15)	5.96 (1.45–24.55)	0.60 (0.14–2.55)

Note- abbreviations: HR: Hazard Ratio, CI: confidence interval, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, CES-D : Center for Epidemiologic Studies- Depression scale, Values in bold are statistically significant, p<0.05