Comorbidity Indices in People with HIV and Considerations for COVID-19 Outcomes.

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Abstract

Objective:

To determine comorbidity indices in persons-with-HIV (PWH) and lifestyle-similar HIV-negative controls.

Design:

Cross-sectional analysis of the Pharmacokinetic and clinical Observations in PeoPle over fifty (POPPY) cohort study in UK and Ireland.

Methods:

The Elixhauser Comorbidity Index (ECI), Charlson Comorbidity Index (CCI) and the Comorbidity Burden Index (CBI) were compared between older PWH and HIV-negative controls using the Mann-Whitney U test; the magnitude of the difference between groups was quantified using the *r* effect size.

Results:

The 699 PWH and 304 HIV-negative controls were predominantly male (87.5% vs. 64.0%), white (86.3% vs. 90.0%) and had median ages of 57 and 58 years, respectively. Among PWH, the median (interquartile range (IQR)) CD4+ T-cell count was 624 (475, 811) cells/µl; 98.7% were on antiretroviral therapy. The median (IQR) ECI was 0 (0, 8) and 0 (-3, 1), CCI was 2 (1, 5) and 1 (0, 1) and CBI 8.6 (2.2, 16.8) and 5.9 (0.6, 10.8), respectively. Whilst all three indices were significantly higher in PWH than in controls (p<0.001 for each), the magnitude of the differences between the two groups were small to medium, with effect sizes (95% confidence interval) of 0.21 (0.16, 0.27), 0.38 (0.32, 0.42) and 0.18 (0.11, 0.23), respectively.

Conclusions

These three comorbidity indices are higher in PWH compared to HIV-negative controls, although the magnitude of differences between groups were small. Differences in the ECI, reportedly associated with poorer COVID-19 outcomes, were driven by more individuals with HIV being within the higher end of the range.

Keywords: HIV; COVID-19; outcomes; comorbidities

Concise Communication

Background

Mortality rates amongst people with Coronavirus Disease 2019 (COVID-19) are challenging to ascertain. For example, many cases may not be captured if individuals have only relatively mild symptoms where people may neither seek nor require medical attention, and cases may not be virologically confirmed with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. In virologically confirmed cases of COVID-19, individuals with multimorbidity and older age appear to have a higher risk of mortality [1]. Specific morbidities such as hypertension, diabetes and cardiovascular disease have all been associated with poor COVID-19 outcomes [2].

Measurement of the presence of multiple comorbidities, or multimorbidity, in an individual can be undertaken via several classification systems. The Elixhauser Comorbidity Index (ECI) [3] and Charlson Comorbidity Index (CCI) [4] are two such classification systems which are significantly associated with both in-hospital and all-cause mortality [5]. A greater ECI has been reported to be associated with higher rates of referral for palliative care and in mortality for people hospitalised with COVID-19 [6, 7].

Higher rates of non-infectious comorbidities have been reported in people with HIV (PWH) compared to lifestyle-similar individuals without HIV [8]. The presence of such comorbidities may theoretically place PWH at higher risk of morbidity and mortality from COVID-19. However, to date no studies have specifically reported higher rates of mortality from COVID-19 in PWH compared to mortality rates from COVID-19 in HIV-negative individuals. Our aim was to determine comorbidity indices in PWH and in lifestyle-similar HIV-negative controls and consider implications of any differences that may exist for the expected outcomes of COVID-19.

Methods

PWH and HIV-negative individuals aged ≥50 years recruited in the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study between April 2013 and January 2016 were included. As previously described in detail [9], PWH were recruited from eight HIV outpatient clinics in UK/Ireland; HIV-negative controls were selected from sexual health centres affiliated to the HIV clinics and were frequency matched on gender, ethnicity, sexual orientation and geographical location to the PWH.

Participants underwent a detailed assessment of comorbidities via a structured interview with trained staff who, where possible, also reviewed hospital notes to validate the presence of

comorbidities [10]. Information provided regarding medical history as well as reasons for any healthcare utilisation and use of (non-antiretroviral) medication over the previous year were used to determine the presence of comorbidities to calculate the ECI [3] and the CCI [4] with scores for these indices obtained using weights proposed by van Walraven et al. [11] and Quan et al. [12], respectively.

In order to assess a comorbidity index associated with patient reported outcomes, we utilised the comorbidity burden index (CBI) which is based on a list of 65 comorbidities (*supplementary material*) with weights empirically derived to reflect the effect of those comorbidities on physical health, measured using the physical health summary scale obtained from the Short Form Health Survey questionnaire [13, 14], and quality of life. Weights were derived using a series of median regression models with physical health quality of life as outcome and each possible pair of comorbidities (one pair at a time) and their interaction as independent variables. The weight of each comorbidity to calculate the CBI was obtained by averaging all the standardised regression coefficients for that comorbidity. Furthermore, regression coefficients for interactions terms were converted into weights in a similar way [15].

We compared the ECI (theoretical range (TR): -19 to 89), CCI (TR: 0 to 24) and CBI (TR: -14 to 110) between PWH and HIV-negative controls using the Mann-Whitney U test and quantified the magnitude of the difference between groups using the r effect size (interpreted as small if $r<0.3$, medium if r between 0.3 and 0.5, and large if $r>0.5$).

Results

A total of 699 PWH and 304 HIV-negative controls were included (*table 1*). Participants were predominantly male (87.5% vs. 64.0% in PWH and controls, respectively), of white ethnicity (86.3% vs. 90.0%) and of homosexual or bisexual orientation (78.4% vs. 47.4%). Median (interquartile range: IQR) age was 57 (53, 62) years in PWH and 58 (53, 63) years in HIV-negative controls. Among PWH, the median (IQR) CD4+ T-cell count was 624 (475, 811) cells/µl, 98.7% were on antiretroviral therapy and 92.1% had a suppressed viral load (<50 copies/ml).

Median (IQR) ECI was 0 (0, 8) in PWH and 0 (-3, 1) in HIV-negative controls (*table 1 and figure 1*). Whilst the median ECI in PWH and HIV-negative controls was similar, overall, PWH had a greater ECI compared to controls (p<0.001) with a small effect size r (95% CI) = 0.21 (0.16, 0.27). CCI also differed significantly in the two groups (p<0.001). Median (IQR) CCI was 2 (1, 5) and 1 (0, 1) in PWH and controls, respectively, with a medium effect size r

(95% CI) = 0.38 (0.32, 0.42). PWH reported a significantly higher CBI [median (IQR) = 8.6 (2.2, 16.8)] compared to HIV-negative controls [median (IQR) = 5.9 (0.6, 10.8), p<0.001], effect size r (95% CI) was small: 0.18 (0.11, 0.23).

Discussion

We assessed three comorbidity indices in PWH and controls and observed these indices to be higher in PWH when compared to our control population. The ECI has been associated with poorer COVID-19 outcomes. Of interest, although the ECI differed between PWH and our control population, median values were similar with the difference between the groups being driven by the range of values, with more individuals with HIV being within the higher end of the range.

So far, little is known regarding the pathogenesis and clinical outcomes of COVID-19 in PWH. To date, available data are limited to case-reports or case-series and a higher incidence of COVID-19 in PWH or higher rates of mortality in PWH [16] have not been observed. Assessment of potential factors for outcomes of COVID-19 in PWH include factors with both positive and negative considerations. Some factors may be associated with positive outcomes in PWH. With regards to incidence of COVID-19, PWH may carry out social distancing and/or isolation more strictly and at an earlier time-point in any given regional epidemic, as individuals with PWH are aware they have an underlying pre-existing clinical condition. This could in certain settings reduce the number of PWH acquiring SARS-CoV-2. With regards to outcomes of COVID-19, in settings with widespread access to antiretroviral therapy, the majority of PWH are on virologically suppressive antiretroviral therapy and have CD4+ lymphocyte counts within normal ranges and therefore may not be at higher risk of more severe COVID-19 [17]. Lastly, some antiretroviral agents to treat HIV may have intrinsic antiviral activity against SARS-CoV-2. Importantly, lopinavir/ritonavir is noted to have antiviral activity against SARS-CoV-2 in laboratory models and could theoretically work as prevention for SARS-CoV-2 acquisition or have beneficial effects on disease outcomes. Ongoing studies are investigating these possibilities however no positive results have been reported thus far [18].

Conversely, several theoretical factors could be associated with poorer outcomes of COVID-19 in PWH. Although, in general, PWH undergo immune-restoration with antiretroviral therapy, it remains unknown whether immune system function returns to levels in HIV-negative individuals and the possibility remains that individuals with low nadir CD4+ lymphocyte counts and other historical legacy effects of HIV-infection may be at greater risk

of adverse outcomes from COVID-19. In addition, given PWH have higher rates of non-infectious co-morbidities and higher comorbidity indices as we have observed, a greater risk of adverse outcomes from COVID-19 could be expected in PWH.

Although the comorbidity indices we have measured are greater in PWH compared to our controls, the differences were generally driven by a skewed distribution in a subset of PWH. Because of regular clinical follow up, the capture of the presence of comorbidities is likely to be greater and more accurate in PWH compared to our control population. Although both PWH and controls in our study are part of a cohort study specifically designed to capture comorbidity details, biases are likely to be present. In general, PWH have clinical monitoring undertaken on at least a six-monthly basis. This monitoring may ascertain the presence of non-infectious comorbidities more accurately when compared to control populations, the majority of whom would not be attending for regular healthcare monitoring. Therefore, the presence of comorbidities and the comorbidity indices we have calculated could be a truer reflection in PWH and may be an under-estimate in our control population.

We have described three comorbidity indices in PWH and controls and highlighted their potential importance. Further conclusions are currently limited by a lack of data on COVID-19 incidence or outcomes within our population. Ongoing monitoring and careful management of comorbidities in PWH are essential with vigilance on outcome measures of COVID-19 amongst PWH over time needed.

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Authors contributions

AW, DDF and CS contributed to the concept and design of this analysis and wrote the first draft of this manuscript. DDF and CS undertook the data analysis. All authors substantially contributed to the writing of the second and further drafts of this manuscript and read and approved the final article.

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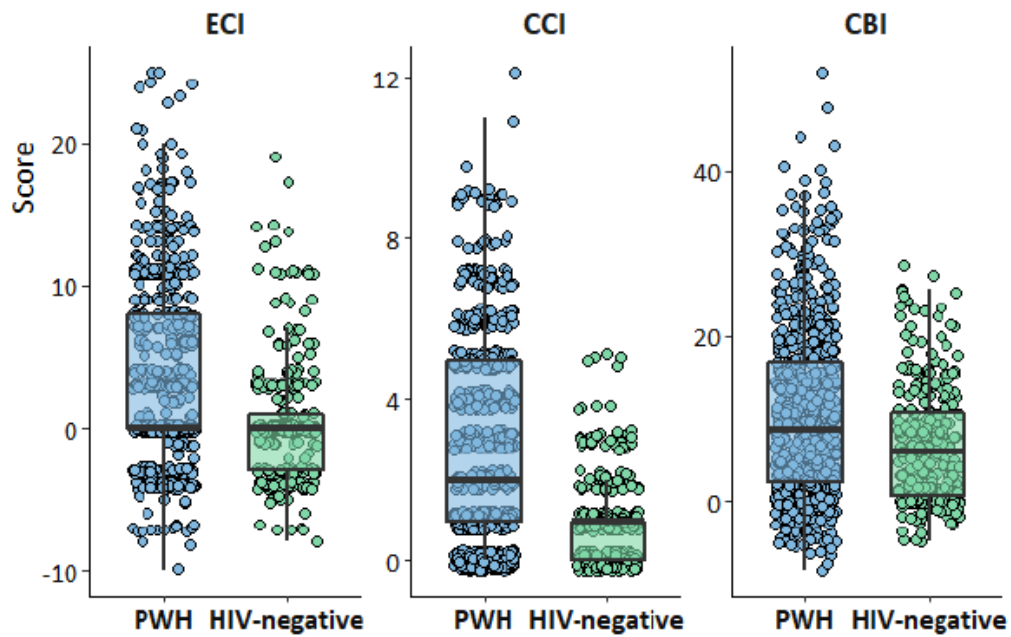
Figure 1: Box plots of comorbidity indices

Abbreviations used: CBI = comorbidity burden index; CCI = Charlson Comorbidity Index;
ECI = Elixhauser Comorbidity Index; PWH = people with HIV.

Table 1: Characteristics of study cohort and comorbidity indices

	PWH	HIV negative	p-value
N	699	304	
Gender, n (%)			<0.001
Male	612 (87.5)	195 (64.0)	
Female	87 (12.5)	109 (36.0)	
Sexuality, n (%)			<0.001
Homo/bisexual	548 (78.4)	144 (47.4)	
Heterosexual	151 (21.6)	160 (52.6)	
Race, n (%)			0.12
White	603 (86.3)	273 (90.0)	
Black African	96 (13.7)	31 (10.0)	
Age (years), median (IQR)	57 (53, 62)	58 (53, 63)	0.06
Marital status, n (%)			<0.001
Single	332 (47.5)	91 (29.9)	
Married/in partnership	264 (37.8)	158 (52.0)	
Other	103 (14.7)	55 (18.1)	
Country of birth			0.35
UK/Ireland	481 (68.8)	223 (73.4)	
Africa	110 (15.7)	41 (13.5)	
Other	108 (15.5)	40 (13.2)	
BMI (kg/m^2), median (IQR)	26 (23, 29)	27 (24, 30)	<0.001
Smoking status, n (%)			0.005
Current	158 (22.6)	42 (13.8)	
Ex-smoker	263 (37.7)	121 (39.8)	
Never smoker/unknown	278 (39.8)	141 (46.4)	
Alcohol consumption, n (%)			0.04
Current	555 (79.4)	262 (86.2)	
Previous drinker	87 (12.5)	24 (7.9)	
Never/unknown	57 (8.2)	18 (5.9)	

Recreational drug use in previous 6 months, n (%)	177 (25.3)	44 (13.9)	<0.001
ECI, median (IQR)	0 (0, 8)	0 (-3, 1)	<0.001
CCI, median (IQR)	2 (1, 5)	1 (0, 1)	<0.001
CBI, median (IQR)	8.6 (2.2, 16.8)	5.9 (0.6, 10.8)	<0.001

Abbreviations used: BMI = body mass index; CBI = comorbidity burden index; CCI = Charlson Comorbidity Index; ECI = Elixhauser Comorbidity Index; IQR = interquartile range; PWH = people with HIV.