COVID-19 severity and in-hospital mortality in an area with high HIV prevalence

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Abstract

Background: HIV is moderate risk factor for developing severe COVID-19 and is associated with increased risk of COVID-19 mortality. HIV infection causes immune dysregulation characterised by progressive lymphopenia, chronic immune activation, immunological senescence, and T cell exhaustion. These changes are partly reversed by effective antiretroviral therapy (ART), which reduces morbidity and mortality in people living with HIV (PWH). We investigated the associations among clinical phenotypes, laboratory biomarkers, and hospitalisation outcomes in a cohort of people hospitalised with COVID-19 in a high HIV prevalence area.

Methods: We conducted a prospective observational cohort study in the Tshwane District Hospital complex in Pretoria, South Africa. We analysed data for patients admitted from April to November 2020, before the SARS-CoV-2 Beta variant-driven second wave. Respiratory disease severity was quantified using the respiratory oxygenation (ROX) score. Analysed biomarkers included full blood counts, differential white cell counts, C-reactive protein (CRP), ferritin, procalcitonin (PCT), D-dimer (DDIM), creatinine, alanine aminotransferase (ALT), CD4 T cell counts, and HIV-1 viral loads (HIVVL).

Results: The analysis included 558 patients, of whom 112 (21.7%) died during admission. The mean age of the cohort was 54 (SD ±16) years, and numbers of males (50.5%) and females (49.5%) were equivalent. A total of 82 (15%) were HIV-positive. PWH were younger (mean age 46 years) than HIV-negative people; most were on ART with a suppressed HIVVL (72%) and the median CD4 count was 159 (IQR 66-397) cells/μL at the time of admission. After adjusting for age, HIV was not associated with significantly increased risk of mortality during hospitalisation (aHR=1.1, 95% CI: 0.6-2.0). Levels of supportive care were similar in HIV-negative patients and PWH. Inflammatory biomarker levels were equivalent in PWH and HIV-negative patients. A total of 15 PWH had detectable HIVVLs (>1000 copies/mL). Detectable HIVVL was associated with higher ROX scores - indicating less severe respiratory disease. In PWH, mortality was associated with higher levels of CRP, ferritin, PCT and DDIM. When compared to HIV-negative patients who died, PWH who died were younger, had higher DDIM levels, and were more likely to have tuberculosis.

Conclusions: HIV *per se* was not associated with substantively increased risk of severe disease, or in-hospital mortality from COVID-19. Respiratory disease was less severe in PWH with detectable HIVVL. Inflammatory biomarker levels were equivalent in PWH and HIV-negative people, regardless of HIVVL. Increased levels of inflammatory biomarkers and DDIM were associated with in-hospital mortality irrespective of HIV status.

Introduction

People living with HIV (PWH) have an increased risk of mortality from infection with respiratory viruses including influenza and human metapneumovirus (1,2). Many studies have reported that PWH, especially those not on antiretroviral therapy (ART) and with a detectable HIV-1 viral load (HIVVL), have a higher risk of COVID-19 related in-hospital mortality (3–5). However, observational cohort studies of hospitalised

patients with COVID-19 have reported that PWH had lower oxygen requirements during their admission. In these studies, patients with detectable HIVVL had lower relative risk of intubation than PWH with suppressed HIVVL (6,7). In a randomised controlled trial, PWH had similar outcomes after initiation of high-flow nasal oxygen or ventilatory support (8). There is still some uncertainty as to whether COVID-19 immunopathology and clinical phenotypes are altered by HIV coinfection.

Current evidence suggests that severe COVID-19 is associated with dysregulation of the monocyte-macrophage response, defective T cells responses, elevated inflammatory cytokines, and hyperactivated neutrophils which culminate in ongoing, inappropriate systemic inflammation which damages pulmonary and other tissues (9–12). People hospitalised with COVID-19, particularly with the more severe spectrum of disease, can develop acute respiratory distress syndrome (ARDS) which is associated with systemic inflammation (13). Established markers of respiratory disease severity in COVID-19 include respiratory oxygenation (ROX) scores and PaO_2/FiO_2 ratios (8,13,14). Treatments which reduce mortality in COVID-19 are anti-inflammatory in nature, with either broad and non-specific targets, like high dose corticosteroids, or targeted, like the interleukin 6 inhibitor, tocilizumab (15).

HIV infection has strong effects on cellular immune phenotypes and function, affecting T and B lymphocytes, and monocytes – all of which are implicated in COVID-19 pathophysiology (16–18). Recently, more evidence has emerged to assess the effect of HIV on cellular immune responses on COVID-19. HIV coinfection does not appear to alter SARS-CoV-2 CD4+ function or phenotypes, but is associated with reduced CXCR3 expression on CD8+ T cells (19,20). Higher HIVVLs are also associated with increased expression of activation markers on CD8+ T cells in COVID-19, which may alter disease manifestations. PWH mount similar SARS-CoV-2 specific antibody responses in acute COVID-19 as HIV-negative people (21). HIV viraemia alters monocyte subpopulation phenotypes, reducing CCR2 and CX3CR1 expression, which may affect their ability to move from blood into tissue. In COVID-19 this may reduce pulmonary inflammation (18).

The majority of PWH analysed in larger cohorts or systematic reviews were on ART, with suppressed HIVVL and high CD4 T cell counts (3,4,22). Consequently, the effect of HIV viraemia and associated immunological changes on the clinical manifestations of COVID-19 remain poorly described. Uncertainty also exists as to the extent to which comorbidities in PWH, such as hypertension, diabetes, or opportunistic infections, contribute to the increased risk of morbidity and mortality.

We investigated whether HIV infection is associated with COVID-19 severity, differences in routinely collected laboratory biomarkers, and mortality after hospitalisation in a well-characterised clinical cohort of patients admitted with COVID-19, in a setting with a high HIV prevalence. Doing so contributes to a better understanding of COVID-19 clinical phenotypes in PWH.

Methods

Cohort description

We conducted a prospective, single centre, observational cohort study of patients admitted to the Tshwane District Hospital Complex (TDH) from April to November 2020.This period encompasses the first COVID-19 wave in Pretoria and predates the widespread prevalence of the SARS-CoV-2 Beta/B.1.351 variant which occurred during the second wave from December 2020 to February 2021. This hospital complex was the primary referral centre for COVID-19 cases in the greater Tshwane area, encompassing a population of approximately three million people, with a HIV prevalence of 10.5% (95% confidence interval [CI] 7.7 – 14.1%) in 2017 (23,24). The hospital could admit 66 adults to general ward care levels (WHO COVID-19 severity score 3 - 4), a dedicated COVID-19 High Care unit (22 adult beds) and an ICU (10 adult beds). The High Care unit admitted patients in need of dialysis, close monitoring on oxygen, high flow nasal oxygen and non-invasive ventilation (WHO score 4 – 5). The ICU was used for patients who were intubated and ventilated (WHO score 6 - 7).

Data including demographic information, comorbidities, date of admission, symptom onset, date of SARS-CoV-2 PCR test, vital signs, level of care, and admission outcome were captured on standardised case report forms (CRF). The CRFs were completed by treating clinicians during patients' admission. Data from the CRFs were entered by research assistants into a REDCap database hosted by the University of Pretoria and reviewed by clinicians involved in the study for accuracy. Hospital admission outcome was coded as survived or died. Survived included patients transferred to other hospitals for further medical care after discharge from the COVID-19 units. Died would include patients with confirmed deaths during hospitalisation for COVID-19. We analysed age as a continuous variable and additionally stratified the cohort into age groups with 20 year-increments.

Admission vital sign data were taken as the worst score within a 48-hour window around the date of admission (admission ± 24 hours). The respiratory oxygenation (ROX) score was calculated for participants with admission vital data (**Figure S1**) (14). The ROX score is a continuous variable which estimates respiratory disease severity by creating a composite score considering the supplemental oxygen concentration, peripheral oxygen saturation, and respiratory rate.

Laboratory biomarker data were extracted from the South African National Health Laboratory Services (NHLS) online data warehouse. We analysed haematology panels (full blood count; differential white cell counts including absolute neutrophil count [ANC], lymphocyte count [ALC], neutrophil-to-lymphocyte ratio [NLR]); organ function biomarkers (creatinine, alanine aminotransferase [ALT]); inflammatory biomarkers (C-reactive protein [CRP], ferritin, procalcitonin [PCT]); and D-dimer (DDIM). Laboratory biomarkers were aggregated as median values for admission ± 24 hours. We analysed CD4+ T cell counts taken during admission. CD4+ T cell counts were stratified at 200 cells/μL into higher (equal to, or above, 200 cells/μL) and lower (below 200 cells/μL) CD4 counts. Plasma HIVVL was assessed from the previous 12 months and during admission, with the most recent value being used for this analysis. HIVVLs were stratified at 1000 copies/mL into detectable (equal to, or above, 1000 copies/mL) and suppressed (below 1000 copies/mL).

Statistical analysis

Data were analysed in R studio (25–29). Baseline characteristics of participants were summarised as means and standard deviations (SD), medians and interquartile ranges (IQR), and counts with percentages as appropriate. Pairwise comparisons of continuous variables were done using Mann-Whitney (MW) U tests or T tests, dependent on the variables' distribution. Comparison of proportions was performed using chi-squared tests, or fishers exact test. Correlations were analysed by Spearman Rank or Pearsons correlation coefficients - dependent on the variable's distribution. The sensitivity and specificity of variables' ability to predict higher levels of supportive care were calculated using Area Under the Receiver Operating Characteristic curve (AUROC). An AUROC cut-off of 0.7 was used to decide if a variable had good predictive ability for a specified outcome.

The association between age and comorbidities was analysed by logistic regression models, with age treated as a continuous variable. Univariate survival analysis was analysed by Kaplan-Meier survival curves with hypothesis testing via log rank tests. Multivariable survival analysis was done using Cox regression models. Schoenfield residuals were used to test for violation of the proportional hazard's assumption. Markers of disease severity, including ROX scores, and laboratory biomarkers were used to stratify the cohort into mutually exclusive tertiles of comparable size.

Ethical approval

Ethics approval was granted by the University of Pretoria's Faculty of Health Sciences Research Ethics Committee, and permission obtained from the institutional authorities to collect clinical data from patients admitted to the Tshwane District Hospital complex. Protocol ethics reference number: 637/2020.

Results

Cohort description

A total of 558 patient records were analysed (**Table 1**). The mean age of this cohort was 54 (standard deviation [SD] ±16) years with equivalent numbers of male (49.5%) and female (50.5%) patients. Hypertension and diabetes were the most common comorbidities, at 55% and 41% respectively. Younger patients were more likely to be HIV-positive at admission (Age and HIV: OR = 0.96, 95% CI: 0.94-0.97, *P*<0.001), and older patients were more likely to have non-communicable comorbidities including hypertension (OR = 1.07, 95% CI: 1.06-1.09, *P*<0.001), diabetes (OR = 1.03, 95% CI: 1.02-1.04, *P*<0.001), cardiovascular disease (OR = 1.04, 95% CI: 1.03–1.06, *P*<0.001) and chronic kidney disease (OR = 1.02, 95% CI: 1.0-1.04, *P*=0.03) (**Figure 1**).

A total of 82 PWH were admitted during this period (15% of cohort). PWH were younger than HIV-negative patients and were less likely to have hypertension or CVD (**Table 2**). PWH were more likely to have a previous, or current, diagnosis of tuberculosis (TB), but the number of patients with active TB was small (n=14). CD4 counts were available for 56 (68.3%) patients, and the median CD4 count was 159 (IQR: 66-397) cells/μL. A total of 32/56 (61.5%) PWH had CD4 counts below 200 cells/μL. HIVVLs were available for 52 (63.4%), and the median HIVVL was 59 789 (IQR: 9 417-194 534) copies/mL. HIVVLs were

suppressed in 37/52 (71.2%). The median duration of symptoms before admission was slightly longer in PWH (8.4 days vs 7.1 days, *P*=0.04). There was no difference in the proportion of symptoms reported at admission, with cough and dyspnoea the most common (**Figure 2**) (Chi-squared *P*>0.05 for all comparisons).

Table 1: Cohort demographics, admission vital signs and biomarker levels

COVID-19 hospital cohort (n = 558)		Missing n (%)
Age (mean (SD))	54 (16)	-
Male n (%)	282 (50.5)	-
Hypertension n (%)	304 (54.5)	-
Diabetes n (%)	227 (40.7)	-
Cardiovascular disease n (%)	75 (13.4)	-
Chronic kidney disease n (%)	54 (9.7)	-
Cancer in past five years n (%)	13 (2.3)	-
Overweight n (%)	124 (22.2)	-
General ward n (%)	418 (75.9)	7 (1.3)
High Care n (%)	85 (15.4)	7 (1.3)
ICU n (%)	48 (8.7)	7 (1.3)
Died n (%)	121 (21.9)	6 (1.1)
Received steroids n (%)	432 (78%)	7 (1.3)
HIV positive n (%)	82 (14.7)	-
Past TB diagnosis n (%)	25 (4.5)	-
Active TB diagnosis n (%)	14 (2.5)	-
Days hospitalised (median [IQR])	6 [3 - 10]	-
Respiratory rate bpm (median [IQR])	22 [20 - 25]	21 (3.8)
Estimated FiO_2 % (median [IQR])	0.37 [0.21 - 0.70]	26 (4.7)
Peripheral O_2 saturation % (median [IQR])	93 [90 - 96]	15 (2.7)
ROX score (median [IQR])	8.2 [4.8 - 16.7]	33 (5.9)
Systolic blood pressure mm/Hg (median [IQR])	123 [111 - 136]	18 (3.2)
ANC $x10^{-9}$/L (median [IQR])	6.7 [4.8 - 10.0]	159 (28.5)
ALC $x10^{-9}$/L (median [IQR])	1.1 [0.8 - 1.6]	159 (28.5)
NLR (median [IQR])	6.2 [3.4 - 9.8]	159 (28.5)
CRP mg/L (median [IQR])	108 [46 - 181]	82 (14.7)
Ferritin µg/L (median [IQR])	527 [238 - 1171]	150 (26.9)
PCT µg/L (median [IQR])	0.13 [0.05 - 0.58]	244 (43.7)

DDIM mg/L (median [IQR])	0.88 [0.39 - 1.95]	113 (20.2)
HbA1c % (median [IQR])	7.2 [6.3 - 10.3]	292 (52.3)
Creatinine (median [IQR])	84 [67 - 115]	64 (11.5)
ALT (median [IQR])	32 [20 - 54]	130 (23.3)

Vital signs and laboratory biomarker levels measured at admission (±24 hours). SD = standard deviation. n = sample size. IQR = interquartile range. bpm = beats per minute. FiO_2 = fraction of inspired oxygen. ROX = respiratory oxygenation score. ANC = absolute neutrophil count. ALC = absolute lymphocyte count. NLR = neutrophil: lymphocyte ratio. CRP = C-reactive protein. PCT = procalcitonin. DDIM = D-dimer. ALT = alanine aminotransferase.

ROX scores and laboratory biomarkers are associated with COVID-19 severity and mortality

The median ROX score at admission was 8.2 (IQR: 4.8-16.7). Increasing age was associated with lower ROX scores at admission (correlation of age and ROX score: rho = -0.2, *P*<0.001), and higher DDIM and inflammatory biomarker levels (**Figure 2A-B**). ROX scores, inflammatory biomarkers and DDIM levels showed significant collinearity with each other (**Figure 2B**).

A total of 85 patients required High Care (HC) as their highest level of supportive care and 48 patients needed Intensive Care Unit (ICU) admission. Length of hospitalisation was longer for those admitted to ICU than the general wards (median 16 days vs 5 days, *P*<0.001). In addition, patients admitted to ICU had more severe disease - ROX scores were lower, ANC, PCT, DDIM and ALT levels were significantly higher when compared to patients admitted to HC or general wards (**Table S1**). Consequently, higher ROX scores, ANC, NLR and PCT levels predicted admission to ICU with AUROC > 0.7. ROX scores below 4.5 had the highest specificity at 82% (sensitivity 62%), and PCT above 0.13 the highest sensitivity at 94% (specificity 57%). The mortality rate was 57% for patients admitted to ICU, 24% for High Care, and 17% for general ward admissions (FET *P*<0.001 for ICU vs HC or General wards).

A total of 121 (21.7%) patients died during admission. Increasing age was associated with increased mortality during the admission (**Figure 2C**). A ROX score below six at admission was associated with a two-fold increase in mortality compared to higher ROX scores (aHR = 2.1, 95% CI: 1.2-3.6, *P*=0.01). The tertiles grouping the highest levels of creatinine, CRP, ferritin, NLR and DDIM were also associated with increased mortality (**Figure 3C**). Sex and diabetes were not associated with increased mortality during hospitalisation, but chronic kidney disease was (aHR = 2.4, 95% CI: 1.5-3.9, *P*<0.001). HIV was not associated with significantly increased mortality (aHR = 1.1, 95% CI: 0.6-2.0, *P*=0.14) (**Figure 2C)**.

COVID-19 severity in people living with HIV

Respiratory rates were equivalent between PWH and HIV-negative patients, however PWH needed less oxygen at admission, and had higher peripheral oxygen saturation readings. ROX scores were higher in PWH, but the difference was not significant (**Table 2**). There was also no significant difference in NLR,

CRP, ferritin, PCT, DDIM, ALT, or HbA1C% levels between PWH and HIV-negative patients. Creatinine levels were slightly lower in PWH, when compared to HIV-negative patients. These associations were unchanged in linear regression models which adjusted for age differences in HIV-negative patients and PWH. PWH were as likely as HIV-negative patients to require admission to ICU - 3.7% of PWH vs 9.5% HIV-negative patients admitted to ICU (FET *P*=0.2).

Markers of disease severity in people living with HIV, stratified by CD4 count and HIV-1 viral load

In PWH, a CD4 count below 200 cells/μL was associated with lower odds of having hypertension, diabetes or being on ART (**Table S2**). PWH with CD4 counts below 200 cells/μL had higher HIVVLs, NLRs and DDIM levels (**Figure 3A**) and were more likely to have TB (25% vs 4%, *P*=0.06) when compared to PWH with higher CD4 counts. ROX scores were equivalent between those with higher and lower CD4 counts (**Figure 4A**). Admission rates to HC or ICU were equivalent between PWH with CD4 counts above or below 200 cells/μL.

PWH with detectable HIVVLs were less likely to be on ART (OR = 0.11, 95% CI: 0.01–0.59, *P*=0.003), and had lower median CD4 counts when compared to those with suppressed HIVVLs (34 [IQR: 16-47] vs 256 [IQR: 134-429], MW *P*<0.0001) (**Table S3**). PWH with detectable HIVVLs were younger than those with suppressed HIVVLs (mean age 40 years vs 48 years, T test *P*=0.02) and were less likely to have diabetes (OR = 0.12, 95% CI: 0.003-0.97, *P*=0.04). PWH with detectable HIVVLs had significantly higher ROX scores that those with a suppressed HIVVLs (17.8 [IQR: 10.9-20.5] vs 6.7 [IQR: 4.3-10.1], MW *P*=0.005). Laboratory biomarker levels were not associated with HIVVL (**Figure 3C**). None of the PWH with detectable HIVVLs were admitted to HC or ICU.

Table 2: Summary and comparison of admission variables by HIV status

	HIV-negative n = 476	PWH n = 82	*P*
Age years (mean (SD))	56 (±16)	46 (±12)	**<0.001**
Male n (%)	243 (51.1)	39 (47.6)	0.63
Hypertension n (%)	275 (57.8)	29 (35.4)	**<0.001**
Diabetes n (%)	200 (42.0)	27 (32.9)	0.14
Cardiovascular disease n (%)	73 (15.3)	2 (2.4)	**0.001**
Chronic kidney disease n (%)	47 (9.9)	7 (8.5)	0.84
Cancer in past five years n (%)	10 (2.1)	3 (3.7)	0.42
Overweight n (%)	111 (23.3)	13 (15.9)	0.15
General ward n (%)	354 (75.3)	64 (79.0)	0.2
High Care n (%)	71 (15.1)	14 (17.3)	
ICU n (%)	45 (9.5)	3 (3.7)	
Died n (%)	109 (23.1)	12 (14.8)	0.11
Received steroids n (%)	372 (78.2)	60 (74.0)	0.31
Previous TB diagnosis n (%)	7 (1.5)	18 (22.0)	**<0.001**
Active TB diagnosis n (%)	5 (1.1)	9 (11.0)	**<0.001**
Days hospitalised (median [IQR])	6 [3 - 10]	6 [3 - 10]	0.73
Respiratory rate bpm (median [IQR])	22 [20 - 25]	22 [18 - 25]	0.85
Estimated FiO_2 (median [IQR])	0.40 [0.21 - 0.70]	0.22 [0.21 - 0.58]	0.07
Peripheral O_2 saturation (median [IQR])	93 [90 - 95]	94 [91 - 96]	**0.02**
ROX score (median [IQR])	7.9 [4.7 - 15.9]	9.8 [5.5 - 19.5]	0.21
Systolic blood pressure mm/Hg (median [IQR])	124 [112 - 137]	118 [105 - 130]	**0.001**
ANC $x10^{-9}$/L (median [IQR])	7.0 [4.4 - 10.5]	6.2 [4.2 - 9.2]	0.18
ALC $x10^{-9}$/L (median [IQR])	1.2 [0.8 - 1.6]	1.1 [0.7 - 1.6]	0.54
NLR (median [IQR])	6.2 [3.4 - 10.3]	6.0 [3.5 - 9.2]	0.81
CRP mg/L (median [IQR])	108 [47 - 181]	110 [42 - 183]	0.99
Ferritin µg/L (median [IQR])	520 [232 - 1232]	542 [295 - 1028]	0.87
PCT µg/L (median [IQR])	0.14 [0.05 - 0.59]	0.08 [0.04 - 0.46]	0.33

DDIM mg/L (median [IQR])	0.88 [0.39 - 1.95]	1.03 [0.36 - 2.08]	0.86
HbA1c % (median [IQR])	7.1 [6.3 - 10.3]	7.7 [6.2 - 12.4]	0.39
Creatinine µmol/L (median [IQR])	85 [68 - 115]	78 [61 - 103]	**0.03**
ALT U/L (median [IQR])	33 [20 - 54]	31 [19 - 47]	0.40

Vital signs and biomarker levels measured at admission (±24 hours). *P* values shown for FET for categorical variables, T test (age comparison) and MW test (all other continuous variables). PWH = People living with HIV. SD = standard deviation. n = sample size. IQR = interquartile range. FiO_2 = fraction of inspired oxygen. ROX = respiratory oxygenation score. ANC = absolute neutrophil count. ALC = absolute lymphocyte count. NLR = neutrophil: lymphocyte ratio. CRP = C-reactive protein. PCT = procalcitonin. DDIM = D-dimer. ALT = alanine aminotransferase.

Variables associated with mortality by HIV status

In total, 109/476 (23.1%) HIV-negative patients died during admission. Among HIV-negative patients, those who died were older (mean age 62 vs 52 years, T test *P*<0.001), and more likely to have hypertension (*P*<0.001), diabetes (*P*=0.06), CVD (*P*<0.001), or CKD (*P*<0.001). Respiratory disease severity was significantly worse at admission in HIV-negative patients who died versus those who survived (ROX score: 4.8 vs 9.5, MW *P*<0.001). Mortality in the HIV-negative patients was also associated with higher levels of laboratory biomarkers, higher ANC, lower ALC and higher creatinine levels (MW *P*<0.001).

A total of 12/82 (14.8%) PWH died during admission. PWH who died all had significant HIV-related comorbidities, or other risk factors for COVID-19-related mortality (**Table 3**). Their hospital stay was shorter than those who survived (median of 3 vs 7 days), and HIVVL and CD4 counts were not associated with in-hospital mortality in univariate analyses (Log rank *P*>0.05) (**Figure 3B & D**). Creatinine, CRP, PCT and DDIM levels were higher at admission in PWH who died compared to those who survived (*P*<0.05 for all comparisons). When compared to HIV-negative patients who died, PWH who died had higher DDIM levels at admission (2.3 [IQR: 1.6-5.9] vs 1.5 [IQR:0.9-3.4], MW *P*=0.05), were younger (mean age 49 vs 64, T test *P*=0.001), less likely to be hypertensive (OR=0.23, *P*=0.02) and more likely to have TB (16.7% vs 0.9%, OR=20.3, *P*=0.03).

Table 3: Clinical description of PWH who died during admission

Patient	Age	Sex	Comorbidities	CD4 count (cells/μL)	HIV-1 viral load (IU/mL)	ROX score [1]	HbA1c %
1	70	Male	Hypertension	375	LDL	1.9	-
2	39	Female	Overweight	36	LDL	3.0	6.4
3	35	Female	Active TB [2]	106	-	15.6	-
4	47	Male	Diabetes B-cell lymphoblastic leukaemia	387	LDL	2.7	6
5	54	Male	CKD stage 5	-	-	-	6.8
6	48	Female	Suspected SLE [3]	608	LDL	12.5	-
7	61	Male	CKD stage 5 Epilepsy	159	-	5.7	-
8	28	Male	Chronic HBV HBV viral load = 64 113 IU/mL B cell lymphoma Active TB on treatment at admission	20	3310	10.2	-
9	63	Female	Hypertension Diabetes Obesity CKD stage 3	612	-	3.2	15.7
10	40	Female	Disseminated CMV CMV viral load = 27 000 IU/mL Cavitating pneumonia	44	$1.36x10^6$	20.6	-
11	57	Male	Hypertension Diabetes	577	LDL	8.3	13.3
12	51	Female	Hypertension	429	LDL	-	6.1

	Diabetes
	Previous TB

[1] ROX score at admission. [2] TB treatment started on empirical grounds. [3] Anti-nuclear antibody positive, with bicytopenia, rash and joint pain - admitted for haemoptysis and developed nosocomial SARS-CoV-2 infection. ROX = respiratory oxygenation score. CKD = chronic kidney disease. HBV = Hepatitis B virus. CMV = Cytomegalovirus. LDL = lower than detectable level. – indicates missing values

Discussion

We report a detailed analysis of clinical phenotypes of COVID-19 in hospitalised patients, with and without HIV, and their association with laboratory biomarkers.

PWH had similar levels of COVID-19 severity, whether estimated by levels of supportive care during hospitalisation, ROX scores or laboratory biomarkers when compared to HIV-negative patients. PWH were younger, less likely to be hypertensive, and had lower creatinine levels at admission. PWH with detectable HIVVLs had less severe respiratory disease, with equivalent levels of systemic inflammation as those with suppressed HIVVLs. Similar results have been reported in hospital cohorts from higher income settings (7,30). PWH with suppressed HIVVLs were older, more likely to be on ART, and more likely to have other comorbidities when compared to those with detectable HIVVLs. The prevalence of comorbidities increased with age in this cohort, as has been reported in other studies (3). Therefore, it is possible that the association between respiratory disease severity and HIVVL was confounded by baseline differences in age and comorbidities in PWH, and not necessarily because of HIV viraemia. However, we should not dismiss the possibility that detectable HIV viral replication could alter immune phenotypes such that COVID-19 severity is affected.

Effective ART suppresses viral replication and reverses much of the immunopathology of HIV, but T cell and monocyte phenotypes, as well as levels of systemic immune activation, remain altered for years afterwards (18,31). Monocyte, and cytokines involved in monocyte trafficking are central to the pathophysiology of COVID-19 (11). Monocytes are recruited to tissue by the interaction of their CCR2 receptor and its ligand CCL2, which is dysregulated in severe COVID-19 (9). HIV infection decreases CCR2 expression on monocytes, and this is reversed with suppressive ART (18). Reduced monocyte trafficking to lungs after SARS-CoV-2 infection may reduce later monocyte-derived inflammation in COVID-19, and this may be a mechanism to explain the less severe respiratory disease in PWH with detectable HIVVLs in this study. Currently reported COVID-19 studies have included few PWH with detectable HIVVLs, and more research is needed to determine the effect of HIV-infection on COVID-19 immune responses.

PWH who died often had significant coexisting comorbidities including active TB infection, lymphoma, disseminated cytomegalovirus, autoimmune disease, or other comorbidities, such as hypertension, diabetes, or CKD. PWH who died with suppressed viral loads were older, had higher CD4 counts and had additional comorbidities like hypertension, obesity, and diabetes, while those with detectable HIVVLs had

significant coinfections or HIV-associated malignancies. The sample size of PWH who died was small, and it is therefore difficult to draw statistically supported conclusions on these observations. Many of the larger studies which reported that HIV infection is associated with increased risk of severe COVID-19 and related mortality included a higher proportion of males in their analysis than our study (3,32–34). It is possible that sex and HIV interact with COVID-19 to alter disease phenotypes. Neutrophils isolated from females have greater inflammatory responses to interferon, which may allow for better innate immune antiviral response (35). Males with severe COVID-19 have altered kynurenic acid metabolism which is associated weaker T cell responses (36). Further research should be undertaken to investigate the interaction of sex, age, and HIV infection on immune responses.

This analysis has several limitations: We analysed records for patients admitted to a single tertiary academic medical centre in an urban area, many patients are sent there by referral which may bias admission statistics towards those with more severe disease. Nevertheless, this cohort's prevalence of HIV-infection was within the range for other reported estimates and is likely to be broadly representative of similar hospital cohorts in South Africa.

Strengths of our study include prospective data collection, a validated method for quantifying respiratory disease severity on a continuum, many patients with laboratory biomarkers during admission, and PWH well characterised in terms of other comorbidities. We have generated several hypotheses related to HIV and COVID-19 for future exploration.

Declarations

Data availability

Complete individual patient data and the analysis code in R are available to researchers on reasonable request.

We report no conflict of interests

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Figures

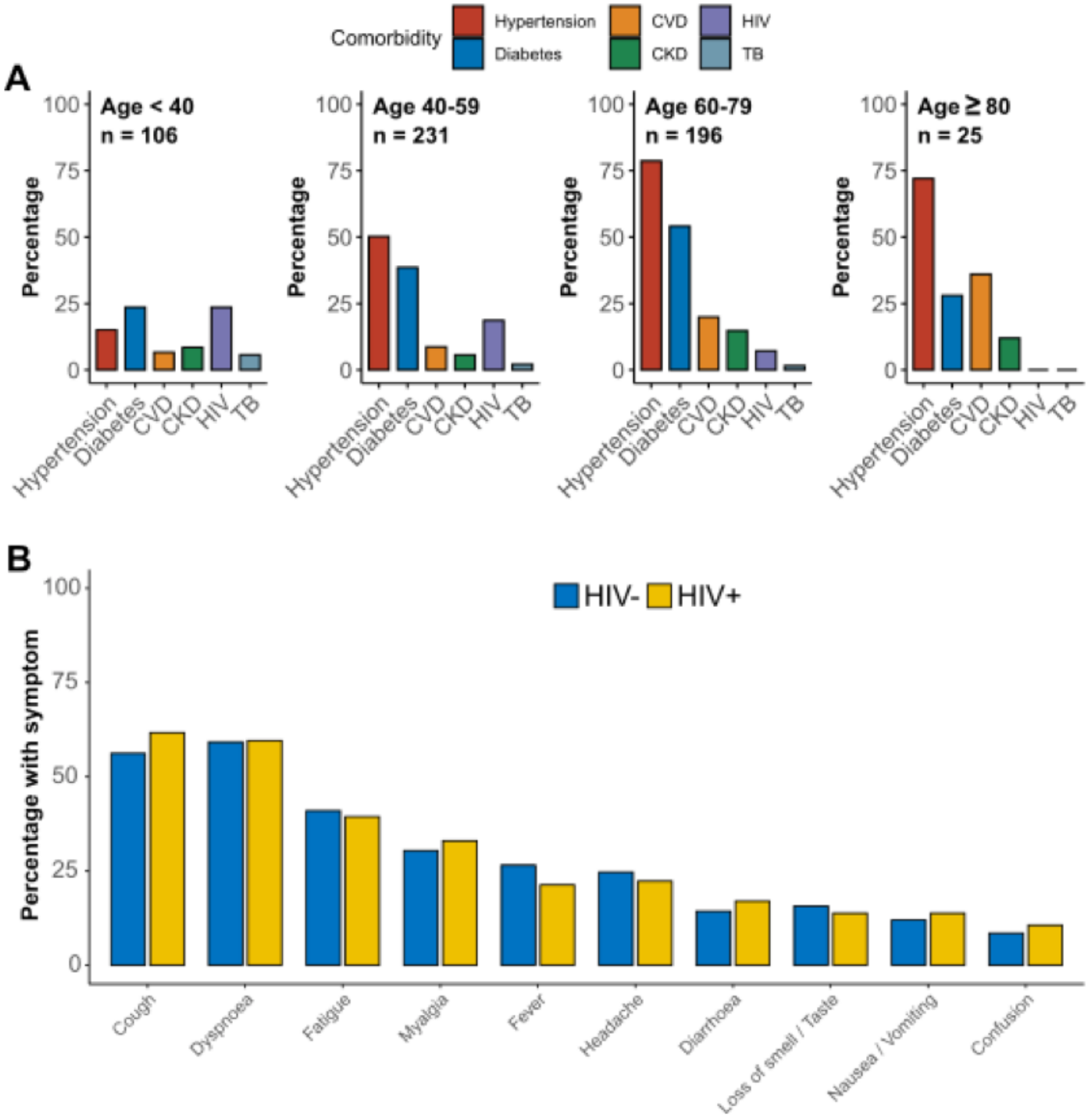

Figure 1

A) The prevalence of comorbidities by age categories is shown. HIV and diabetes were the most common comorbidities in patients younger than 40 years. Prevalence of non-communicable comorbidities increased with age, and HIV prevalence decreased. CVD = cardiovascular disease, CKD = chronic kidney disease. B) No significant differences in symptoms at admission by HIV status (Chi-squared P>0.05 for all pairwise comparisons). Cough and dyspnoea were the most common symptoms at admission.

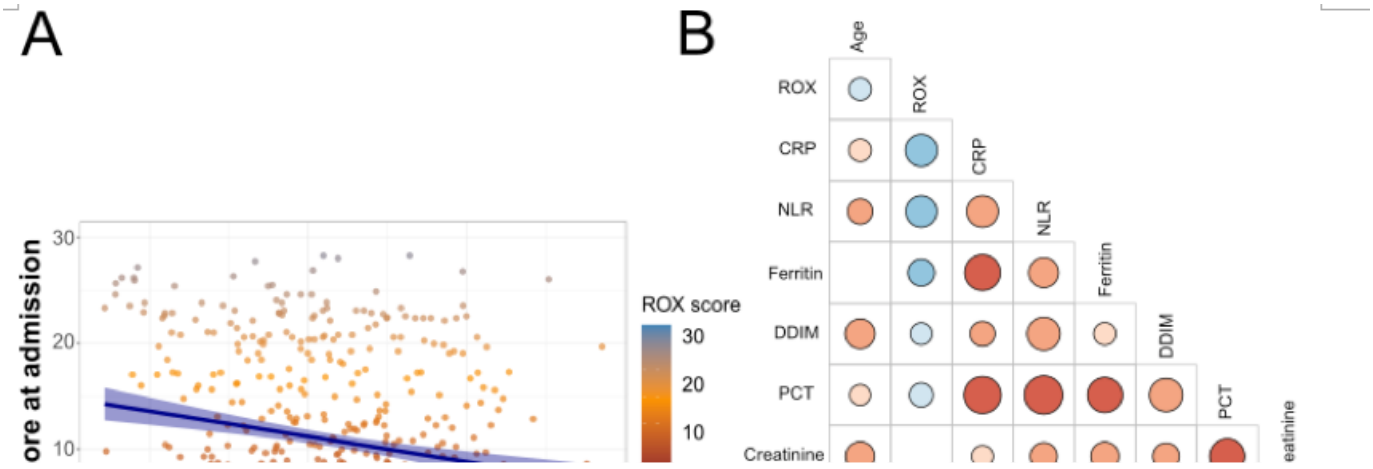

Figure 2

A) Age and ROX scores at admission correlated negatively (rho = -0.2, P<0.001). B) Correlation matrix of biomarkers with age and ROX score, non-significant correlations are shown as blank cells. The size and colour of the circles show the strength and direction of the Spearman correlation coefficients. C) Forest plot of the hazard ratio (HR) and their confidence intervals for variables association with in-hospital

mortality. Age was associated with a strong effect on mortality; therefore, all other HRs are age-adjusted.

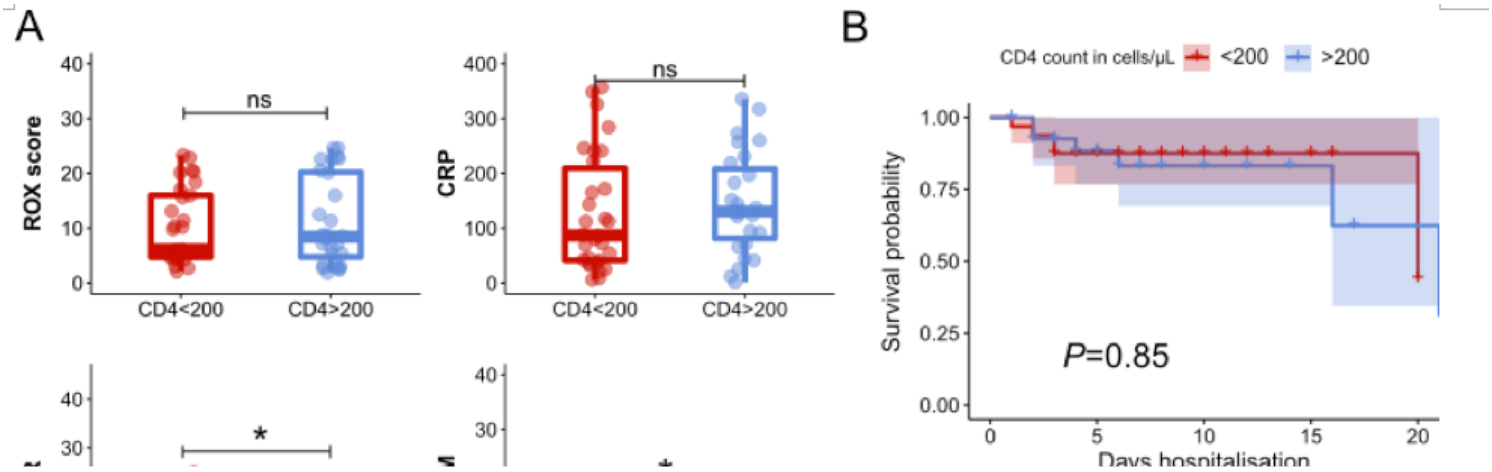

Figure 3

A) Pairwise comparisons for ROX scores, CRP, NLR and DDIM levels are shown for higher and lower CD4 counts. Lower CD4 counts were associated with higher NLR and DDIM levels at admission. B) Kaplan-Meier survival curves are shown for PWH stratified by CD4 count. There was no significant difference in time to death in hospital, logrank P value shown. C) Pairwise comparisons for ROX scores, CRP, NLR and D-dimer levels are shown for PWH by HIVVL. An HIVVL above 1000 copies/mL was associated with significantly higher ROX scores at admission. D) Kaplan-Meier survival curves overlapped for these patients indicating no significant difference in survival, logrank P value shown. * = P<0.05; ** = P<0.01; ns = not significant.

Supplementary Files

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