Risk of COVID-19 in-hospital mortality in people living with HIV compared to general population according to age and CD4 strata: data from the Icona network

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HIGHLIGHTS

- Risk of in-hospital COVID-19 mortality in PLWH and general population was assessed
- -PLWH <65 years with CD4 ≤350 cells/mm^3 are at higher risk of worse COVID-19 outcomes
- This risk is further increased in PLWH <65 years with CD4 count ≤200 cells/mm^3
- The evidence was insufficient for PLWH aged ≥65 years
- PLWH with low CD4 counts should be prioritized for preventive interventions

Risk of COVID-19 in-hospital mortality in people living with HIV compared to general population according to age and CD4 strata: data from the Icona network

Running Title: Outcomes of hospitalized COVID-19 in PLWH

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Key words: SARS-CoV-2; death; hospitalization; immunodepression; people living with HIV

Abstract

Objectives

To study whether people living with HIV (PLWH) are at higher risk of in-hospital COVID-19 mortality compared to general population (GenPop).

Methods

Retrospective study in 19 Italian centres (Feb2020-Nov2022) including hospitalized PLWH and GenPop with SARS-CoV-2 infection. Main outcome: in-hospital mortality. Competing risk analyses by Fine-Gray regression model were used to estimate the association between in-hospital mortality and HIV-status/age.

Results

7,399 COVID-19 patients were included, 239 (3·2%) PLWH, and 7,160 (96·8%) GenPop. By day 40, in-hospital death occurred in 1,283/7,160 (17·9%) among the GenPop and 34/239 (14·2%) among PLWH. After adjusting for potential confounders, compared to GenPop <65 years, a significantly higher risk of death was observed for the GenPop ≥65 [aSHR 1·79 (95%CI 1·39-2·31)], PLWH ≥65 [aSHR 2·16 (95%CI 1·15-4·04)], PLWH <65 with CD4 ≤200 [aSHR 9·69 (95% CI 5·50-17·07)] and PLWH <65 with CD4 201-350 [aSHR 4·37

(95%CI 1·79-10·63)], whereas no evidence for a difference for PLWH <65 with CD4 >350 [aSHR 1·11 (95%CI 0·41-2·99)].

Conclusions

In PLWH aged <65 years a CD4 ≤350 rather than HIV itself seems the driver for the observed higher risk of in-hospital mortality. We cannot however rule out that HIV-infection per se is the risk factor in those aged ≥65 years.

1.0 Introduction

Since the early phase of SARS-CoV-2 pandemic it has been questioned which groups of subjects were at higher risk of worse COVID-19 outcomes. This would have allowed firstly to implement specific preventing interventions, allocate therapeutic resources, and in the later phases of the pandemic prioritize COVID-19 vaccination. Demographic factors shortly appeared to be the main determinants of COVID-19 outcomes, with older age, male sex and social deprivation as strongly associated with hospitalization and death [1]. Comorbidities appeared also to be associated with an increased risk of in-hospital death for COVID-19 during the first phase of the pandemic [1-4]. Initially, there was conflicting evidence regarding the risk of worse COVID-19 outcomes in subjects under immunosuppressive treatment or affected by immune system disorders [5]. Among these, people living with HIV (PLWH) were initially investigated by several case series and small cohort studies [6-11]. All these studies were limited by the absence of a comparison with the general population, an adequate study design to control for confounders or enough power to estimate a consistent effect of HIV infection on COVID-19 major outcomes [6-11]. Taken together, these preliminary observations contributed to the speculation that HIV does not predispose to more severe disease or higher mortality rate especially in well-controlled PLWH, although several open questions remained in those with advanced HIV infection [12]. Subsequently, several

large observational studies conducted in UK [13, 14] South Africa [15], US [16] and on the WHO Global Clinical Platform [17] found that PLWH appeared to be at higher risk of death when compared to the general population. Nevertheless, all these studies investigated the HIV status total effect as a main exposure of interest without trying to single out the crucial confounding and potential interaction with age and CD4 count in PLWH [18]. A study conducted by Dandachi et al was the first to show a potential association between a lo w CD4 cell count (<200 cell/mm^3) and the risk of a composite clinical outcome of disease severity in COVID-19 patients [19]. In addition, most of these previous studies were conducted during the first pandemic period [6-17].

With this analysis we aimed to evaluate the risk of day-40 in-hospital mortality attributable to HIV in individuals admitted to the hospital with COVID-19, after specifically disentangling the confounding and effect modifying effects of age and CD4 count in PLWH.

2.0 Methods

2.1 Study design

This was a retrospective observational multi- centre study conducted in 19 centres from the Italian Cohort Naïve Antiretroviral (ICONA) network [20] covering 9 Italian regions.

2.2 Study population

PLWH aged 18 or older seen for care at one of the Icona Network participating sites who were admitted to the hospital between the 20th February 2020 and 30th November 2022 with a diagnosis of SARS-CoV-2 infection (documented by means of a positive real-time-polymerase chain reaction on nasopharyngeal swabs or lower respiratory tract specimens or positive SARS-CoV-2 antigenic test) and with signs and/or symptoms related to COVID-19 were included. Some participating sites also contributed a sample of the general population

who were also admitted to the same hospitals over the same time period with a diagnosis of SARS-CoV-2 infection (see Supplementary Table 1).

2.3 Data collection

Data were collected by means of *ad hoc* built standardized electronic CRF forms for both PLWH and the general population groups at each of the participating sites. The collected data were the patients' demographic characteristics including biological sex, age and ethnicity; the date, site and region of admission; periods of hospital admission which were categorized in accordance to the circulating variants of concern (VOC) in Italy [WT/Alpha/Gamma (before 15 June 2021) vs Delta (15 June 2021-19 December 2021) vs Omicron (after 20 December 2021) [21]; comorbidities (including cerebrovascular disease, chronic kidney diseases, asthma, chronic obstructive pulmonary disease (COPD), diabetes, autoimmune disorders, cancer, end and non-end stage liver disease, neurological disease and obesity, defined as a body mass index of ≥30 Kg/m^2); pneumonia at hospital admission; disease severity upon hospital admission (PaO2/FiO2) estimated as described by Pandharipande et al [22]; primary vaccination cycle completion before admission; the drugs used to treat COVID-19 (which included hydroxychloroquine, lopinavir/ritonavir, remdesivir, tocilizumab and other immunomodulators, heparin, steroids, molnupiravir, nirmatrelvir/ritonavir and monoclonal antibodies); laboratory parameters (including C-reactive protein); maximum level of oxygen supply required during the hospitalization (including no oxygen requirement, low flow, high flow, Continuous Positive Airway Pressure or Non Invasive Ventilation and mechanical ventilation) and the hospitalisation outcome (death, discharge, or transfer to other facilities).

For PLWH the following additional information were also collected: last available CD4 cell count before admission; last available HIV-RNA; antiretroviral regimen composition if they were receiving ART; previous AIDS defining event and the main reason of death categorized as COVID-19, AIDS, cancer and end-stage liver disease (ESLD).

2.4 Outcome

The main outcome of interest was time from hospital admission to in-hospital death by 40 days.

2.5 Statistical Analysis

Descriptive statistics were used to show proportions for categorical variables, and median values with their interquartile range (IQR) for continuous variables by exposure groups. The baseline demographic and clinical-epidemiological characteristics of PLWH and the general population group were compared using the $\chi 2$ or, when necessary, Fisher's exact test in the case of categorical variables, and Wilcoxon's rank-sum test in the case of continuous variables.

A categorical variable was constructed for the exposure of interest encompassing the following 6 groups: i) the general population group <65 years, ii) the general population group ≥65, iii) PLWH aged <65 and CD4 >350 cells/mm^3, iv) PLWH aged <65 and CD4 201-350 cells/mm^3, v) PLWH aged <65 and CD4 ≤200 cells/mm^3 and finally vi) PLWH ≥65 years.

In the survival analysis, follow-up accrued from the date of hospital admission to in-hospital death or hospital discharge. Competing risks Kaplan-Meier curves were used to estimate the cumulative probability of in-hospital mortality in hospitalized COVID-19 patients and compare the rates across the 6 groups. These curves were calculated after extending the follow-up of participants who have been discharged alive before day 40 up to day 40.

Unadjusted and adjusted Fine-Gray regression models have been used to estimate the association between the 6 levels' exposure and COVID-19 in-hospital mortality. In this analysis, hospital-discharges due to cure which occurred before day 40 were handled as a competing event.

The sources of potential confounding were controlled for in the statistical analysis by including in the model age, sex, ethnicity, comorbidities (immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease and lung disease) and region of Italy of the participating site which were sufficient to block all measured confounding pathways under the assumptions shown in the directed acyclic graph (DAG) in Supplementary Figure 1. Although calendar time of hospital admission is not a confounding factor under our assumptions was a strong predictor of death and therefore was further included to improve the efficiency of the model.

The following sensitivity analyses were also performed: i) after restricting the analysis to participants presenting at hospital admission with a documented pneumonia and/or a PaO2/FiO2 <300. This would minimise the potential bias related to different threshold in hospital admission for PLWH and the general population group, ii) after restricting the analysis to sites contributing both PLWH and the general population sample. This would minimise the potential bias introduced by the non-concurrent enrolment of exposed and unexposed subjects. For this sensitivity analysis, the model has been adjusted for participating centre of enrolment instead of the region of Italy, iii) after rerunning the model under the alternative assumption that all other co-morbidities already present at the time of hospital admission besides asthma and COPD are not confounding in the causal pathway to mortality. The critical assumption for this analysis is that the comorbidity was developed after having acquired HIV, iv) after restricting the analysis to the Omicron period. This would allow to assess the potential effect of CD4 cell count in the context of a less pathogenic virus such as the period of circulation of Omicron variant of concern, v) after restricting the analysis to subjects how completed a primary COVID-19 vaccination cycle (defined as ≥2 COVID-19 vaccine shot before hospital admission). This would allow to assess the potential

effect modification of vaccination status on COVID-19 in-hospital mortality according to CD4 cell count strata.

2.6 Ethical statement and IRB approval

The ICONA Foundation study was approved by the individual Ethic Committees of participating centres, all involved in studies concerning clinical data of hospitalized patients with COVID-19; sensitive data from patients were seen only in aggregate form. All patients signed a consent form to participate in the single center cohorts in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amended in October 2013). All information, including virological and therapeutic data, was recorded and merged into a pseudo-anonymized database.

2.7 Role of the funding source

The present study was supported by Gilead Fellowship Program 2021· The Icona Foundation wrote the study project, collected and analysed the data and finalized the drafting of the paper. The funder had no role in data collection, analysis, and interpretation, or in writing the paper.

3.0 Results

3.1 Characteristics of the study population at hospital entry

This analysis includes 7,399 COVID-19 hospitalized patients: 239 (3·2%) PLWH and 7,160 (96·8%) participants who were HIV negative or with unknown serostatus (general population group). Characteristics of the study population are reported in Table 1. Male sex at birth was prevalent among PLWH in all the age and CD4 strata when compared to the general population group ($p<0·001$), whereas a lower proportion of Caucasian was observed among PLWH in all age and CD4 strata apart from PLWH aged ≥65 years in which the prevalence

of this ethnicity appeared to be comparable with that of the general population counterpart (97·7% and 96%, respectively).

PLWH less frequently presented with pneumonia and/or PaO2/FiO2 <300 at hospital admission in all age and CD4 cell strata when compared to the general population group (p<0·001). PLWH had a median CD4 cell count of 395 (IQR 161-620) cells/mm^3 with a proportion of subjects with an HIV-RNA <50 cp/mL of 76·1% (Table 2).

3.2 Treatment and respiratory support in follow-up

When compared to the general population group, a higher proportion of PLWH did not require oxygen supply during the hospital stay in all age and CD4 strata (p<0·001) (Supplementary Table 2). The highest proportion of subjects requiring intensive care assistance was observed among PLWH <65 years with CD4 cell count ≤200 cell/mm^3 (19·4%) followed by those aged <65 years in the general population (10·5%). Regarding pharmaceutical interventions during the hospitalization, PLWH were exposed with a lower frequency to heparin in all age and CD4 strata (p<0·001), steroids (p<0·001) and hydroxychloroquine (p<0·001) when compared to the general population group, whereas no evidence for a difference in remdesivir use was observed (p=0·639), such as for monoclonal antibodies (p=0·718), early antiviral treatments (p=0·146), immunomodulant agents (p=0·149).

3.3 COVID-19 in-hospital outcomes

The longest median period of hospitalization, when simply calculated as the total of days spent in hospital was observed among PLWH <65 years with CD4 cell count ≤200 cell/mm^3 [19 days (IQR 11-31)] followed by PLWH <65 years with CD4 cell count 200-350 cell/mm^3 [16 days (IQR 9-22)] and those aged ≥65 years in the general population [14 days (IQR 8-23)]. Thirty-four out of 239 (14·2%) PLWH and 1,283 out of 7,160 (17·9%) patients of the general population group died during the hospitalization. Among PLWH, 26 (76·5%) deaths

were deemed as directly related to COVID-19 whereas 4 (11·8%) were AIDS-related, 2 (5·9%) cancer-related and 2 (5·9%) ESLD related. The distribution of COVID-19-attributable death in PLWH according to age and CD4 cell count strata is reported in Supplementary Table 3. Individual causes of death were not available for the general population group. The Kaplan-Meier curves in which death and discharged have been handled as competing events are depicted in Figure 1.

In the Fine-Gray regression model main analysis, after adjusting for potential confounders (age, sex at birth, ethnicity, region of enrolment, immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, obesity and lung disease) as well as calendar period of hospital admission, when compared to the general population group <65 years, a significantly higher risk of death was observed for the general population ≥65 years [aSHR 1·79 (95%CI 1·39-2·31)], PLWH ≥65 years [aSHR 2·16 (95%CI 1·15-4·04)], PLWH <65 years with CD4 ≤200 cell/mm^3 [aSHR 9·69 (95% CI 5·50-17·07)] and PLWH <65 years with CD4 201-350 cell/mm^3 [aSHR 4·37 (95%CI 1·79-10·63)], whereas no evidence for a difference for PLWH <65 with CD4 >350 cell/mm^3 [aSHR 1·11 (95%CI 0·41-2·99)] (Table 3). Consistent results were obtained in the i), ii) and iii) sensitivity analyses (Table 4). After restricting the analyses to subjects admitted during the Omicron period (iv) and to those who completed a primary COVID-19 vaccination cycle before hospital admission (v), when compared to the general population group <65 years, a significantly higher risk of death was observed for PLWH <65 years with CD4 ≤200 cell/mm^3 [aSHR 9·06 (95% CI 2·87-28·65) and 15·85 (95% CI 5·03-49·93), respectively] and PLWH <65 years with CD4 201-350 cell/mm^3 [aSHR 24·13 (95%CI 2·70-215·83) and 11·60 (95% CI 2·08-64·78), respectively].

4.0 Discussion

Our analysis shows that among hospitalized subjects for COVID-19, PLWH aged <65 years with a CD4 cell count <350 cells/mm^3 had a higher risk of in-hospital mortality when compared to the general population group of similar age, whereas there was no evidence for a difference for PLWH with a CD4 count >350 cells/mm^3. Importantly, there was a clear dose-response associated with CD4 count with the risk being even higher in those with a CD4 count <200 cells/mm^3. The evidence was insufficient for PLWH aged ≥65 years. Age was the strongest predictor of mortality regardless of HIV status.

The question of whether HIV status confers a higher risk of severe COVID-19 disease was highly debated during the first pandemic period. Nevertheless, the first reports and case series were undermined by the absence of an adequate sample size which guaranteed adequate power to estimate the possible effect of HIV status on the risk of mortality [6-11]. What was clear from these first reports was that, in the hospitalized setting, the demographic characteristics of PLWH were different from that of the general population with a predominance of younger males [6-11]. This difference was observed through the course of the pandemic in subsequent large observational cohort studies [13-17] and confirmed in our study.

These early studies found no association between HIV and risk of severe outcomes after hospitalization, but their results might have been confounded by age [6-11]. This pitfall was firstly addressed by Geretti et al in a large UK dataset including 122 PLWH and 47,470 HIV unexposed subjects hospitalized with COVID-19 in which the authors found a higher risk of day-28 mortality in HIV-negative individuals in the unadjusted analysis which was reversed after controlling for age (47% higher risk in PLWH) [14]. Interestingly, age appeared to be an effect-measure modifier as there was an almost 3-fold higher risk for PLWH when compared to the HIV-negative group when restricted to participants aged 60 or older (aHR 2·87; 95% CI 1·70–4·84) [14]. In addition, in another study conducted in South Africa a greater

proportion of COVID-19 deaths was observed in PLWH aged <50 years when compared to HIV-negative subjects (39% *vs* 13·1%, respectively) [23]. Other, population-level studies performed in the UK (OpenSAFELY [13]), South Africa [15, 23] and the USA [24] estimated an increased risk of COVID-19 mortality for PLWH when compared to the general population [aHR 2·59 (95% CI 1·74-3·84), aHR 2·14 (95% CI 1·70–2·70) and aOR 1·29 (1·16–1·44), respectively]. However, even in recent years, results remained conflicting as in two other large studies conducted in the USA [25-27] and in Spain [28] in 2020-21, conversely, the authors found no association between HIV status and COVID-19 death.

Of note, in the majority of these previous studies no information was provided regarding the immunological status of PLWH and thus it was unclear if this increased risk could be attributable to low CD4 count. Our data provide a potential explanation of what has been previously observed in subjects aged <65 years. In particular, we found that, after controlling for potential confounders, PLWH aged <65 years with a CD4 cell count 201-350 cell/mm^3 and ≤200 cell/mm^3 were respectively at 4- and 9-fold higher risk of in-hospital death when compared to the general population group of similar age, whereas there was no evidence for a difference when considering PLWH with a CD4 count >350 cells/mm^3. Results were confirmed in sensitivity analyses aimed to minimise a number of potential biases. In addition, we found no evidence for a difference in mortality when comparing our general population group aged <65 years with both PLWH and the general population group aged ≥65, although with large uncertainty around these estimates. There are two potential explanations for these latter secondary findings. First, it is possible that the effect of HIV on mortality is even larger in the age strata of those aged 65 or older but our study was underpowered to detect this interaction. Indeed, a previous study has shown that the effect of HIV might be exacerbated with older age [24]. Conversely, it is also possible that HIV has a smaller impact on mortality in older subjects where the course of the disease is more severe, and the outcome is mainly

age-related. This second hypothesis is also consistent with the fact that in the general population the outcome of younger subjects significantly improved overtime, but this was not seen in older COVID-19 patients [29].

One key issue when analysing data coming from the observational setting is how to minimize the effect of confounding. The set of confounders used in previous analyses typically included: sex, ethnicity, age, baseline date, a number of underlying conditions (i.e., diabetes, tuberculosis, chronic kidney diseases, pulmonary diseases, and malignancies) and COVID-19 disease severity at presentation although these were slightly different from analysis to analysis and different from those used by us in the main analysis [14, 17]. This makes the comparison between results more difficult.

Nevertheless, our results are consistent with some of those already published. For instance, in a sub-group analysis of the above-mentioned population study conducted in South Africa the authors found that PLWH with a CD4 cell count <200 cell/mmc had a higher risk of death when compared to HIV negative subjects [2·36 (95% CI 1·47–3·78)] and to PLWH with a CD4 cell count >350 cell/mmc [1·97 (95% CI 1·14–3·40)] [23]. Similarly, in the analysis by Yang et al after adjusting for demographics, lifestyle factors, comorbidities, and month of COVID-19 diagnosis, a CD4 <200 was associated with a higher odds of death [aOR 3·10 vs PLHW with CD4 count >500 cell/mm3 (95% CI 1·06–9·13)] [24], as well as in the analysis by Boulle et al where being viraemic or having a CD4 <200 was associated with a higher hazard rate of death when compared to HIV negative subjects [3·35 (95% CI 1·83-6·12)] [23]. With our analysis we were able to add a piece to this puzzle by investigating the CD4 cell strata 201-350 cell/mm^3 and showing that also in these strata the risk of in-hospital death was significantly higher when compared to the general population counterpart of similar age. A causal relationship between immunosuppression status and risk of death in PLWH vs the general population group was further supported by the dose-response relationship with level

of CD4 count with the difference in risk more than doubling when investigating the risk in the 201-350 vs ≤200 cell/mm^3 strata (aSHR 4·37 and 9·69, respectively). In addition, according to the sensitivity analyses restricted to the Omicron period and to vaccinated subjects, PLWH aged <65 years with a CD4 cell count <350 cell count cell/mm^3 were confirmed to be at higher risk of in-hospital death when compared to the general population group <65 years. COVID-19 vaccination and the Omicron period seem to act as effect modifiers with a potential further increased risk in a context of a less pathogenetic virus (such as Omicron variant) or in vaccinated subjects. Nevertheless, these findings should be look with caution considering the low number of events observed in this sensitivity analysis and the wide confidence intervals provided by the models.

Limitations

Our study has a number of limitations.

First of all, a significant proportion of centres were not able to provide unexposed (HIV-negative or unknown serostatus) subjects. However, we performed a sensitivity analysis after restricting to sites who contributed both PLWH and the general population sample and the results were similar.

Second, because the outcome was all-cause mortality it is possible that some of the deaths were not COVID-19 related. However, results were similar in a sensitivity analysis which was restricted to participants with pneumonia and/or PaO2/FiO2<300 mmHg at hospital admission. However, it has to be noted that PaO2/FiO2 was available only for a subset of the study population so we cannot rule out potential selection bias in this sensitivity analysis. Nevertheless, we observed that most of PLWH who died in-hospital (77%) had COVID-19 reported as the leading cause of death. Moreover, the proportion of subjects who died for a reason other than COVID-19 was equally distributed among PLWH CD4 strata.

Third, the use of hospitalized individuals might not fully reflect the HIV-related risk of adverse COVID-19 outcomes. In particular, because PLWH are expected to be a high-risk population, it might be more likely that they will be admitted with a higher frequency also when presenting with a mild COVID-19 when compared to the general population in which only individuals with more severe symptoms are typically admitted. Nevertheless, we tried to partially address this limitation by performing a sensitivity analysis restricted only to subjects with a PaO2/FiO2 <300 and the results of this sensitivity analysis were consistent with the estimates provided by the main analysis.

Fourth, the significant differences between PLWH and general population observed in term of COVID-19 treatments, in particular heparin and steroids, could be explained by the different between groups severity observed at hospital admissions. As mentioned above PLWH could have been admitted with less severe forms of COVID-19 when compared to the general population but they could have been managed as a high-risk population and this could explain the similar proportion of antiviral treatments between PLWH and general population although the disease severity at admission was different. We have tried to partially address this issue by performing our sensitivity analysis restricted to those with a PaO2/FiO2 <300.

Finally, our results are valid under the usual assumption of a correctly specified model and no unmeasured or residual confounding. As far as residual measured confounding is concerned, our main analysis differs from most of the others because did not control for many underlying conditions at hospital admission. Unfortunately, in absence of exact information on temporality, there is no analytic tool that will tell us whether, for example, malignancies or cerebrum/vascular disease are confounders or mediators of our association of interest and the prevalence of cerebrum/vascular disease was imbalanced between PLWH and the general population sample. Therefore, we assumed that they were confounders in the main analysis and mediators in a sensitivity analysis (which consequently not adjusted for these factors) and

the results were again similar. Calendar period (which also incapsulates the predominantly circulating VoC with variable pathogenicity) was strongly predictive of mortality and was further included in the model to increase efficiency. Vaccination is also an important predictor of mortality, but HIV is a factor potentially associated with an increased probability of vaccination. Under this assumption vaccination is a mediator in the causal pathway between HIV and risk of death and this is why has not been adjusted for in the models. Also, vaccination and natural infection were not included because we could not exclude information bias for these variables. Finally, index of deprivation, which was found to be linked to COVID-19 hard outcomes in population-level studies, is a potential unmeasured source of confounding.

Nevertheless, our study has also some important strengths. First of all, it covers a long period of the COVID-19 pandemic (from 2020 until the end of 2022) so that extends previous findings to the era of infections with less pathogenic strains of SARS-CoV-2· In addition, because we were able to collect data on immune-virological characteristics of PLWH this allowed us to provide a deeper investigation of the possible determinants of mortality and suggest a possible explanation (i.e. specific thresholds of HIV-induced immunosuppression).

5.0 Conclusion

In conclusion, our analysis further clarifies the impact of HIV on the risk of mortality after hospital admission for COVID-19 disease by highlighting the role of immunosuppression (CD4 $\leq$350 cells/m^3) in PLWH aged <65 years. We cannot however rule out that HIV-infection per se is the risk factor in those aged $\geq$65 years. Our data further support the notion that PLWH aged <65 years with CD4 count $\leq$350 cells/mm^3 and especially those with <200 cells/m^3 should be prioritised for access to infection preventing interventions and early treatments.

Declaration of Interest

AGiacomelli reports speakers' honoraria for ViiV Healthcare and Gilead Sciences, advisor for Janssen-Cilag and Mylan; RG reports payments to her institution from Gilead Sciences, speakers' honoraria for ViiV Healthcare, Merck Sharp and Dohme and Gilead Sciences, advisor for Thera Technologies, Janssen-Cilag and Gilead Sciences; GR reports consultancies/advisory from ViiV Helathcare, GSK, Merck Sharp and Dohme and Gilead Sciences; AGori received speaker's honoraria and feesfor attending advisory boards from ViiVHealthcare, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer and Novartis and received researchgrants from ViiV, Bristol-Myers Squibb, and Gilead; AM received speakers' honoraria from Gilead Sciences, and ViiV Healthcare, travel fee from Viiv Healthcare and participated in advisory boards sponsored by ViiV Healthcare; AV received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served an advisor for Janssen-Cilag; MM received speakers' honoraria from ViiV Healthcare; LT reports consultancies/advisory from Viiv Healthcare, Gilead Sciences and Janssen-Cilag and institutional fellowship from Gilead Sciences; GMarchetti participated to advisory boards of Gilead Sciences, ViiV Healthcare, Angelini and Janssen-Cilag, and received travel grants from ViiV-Healthcare and Janssen-Cilag; AdM participated in advisory board of Gilead Sciences, ViiV Healthcare, Merck Sharp and Dohme, Pfizer and GSK and reports research grant from Gilead Science, ViiV Healthcare, Merck Sharp and Dohme, GSK and Janssen-Cilag; AA received Research grants from Gilead Sciences, AstraZeneca, ViiV Healthcare and Honoraria from Gilead Science, AstraZeneca, GSK, Pfizer, Merck Sharp and Dohme, Moderna, Mylan, Janssen-Cilag, ViiV Healthcare ; AT, SDB, SA, GMancarella, FMF, ADV, VM, MA and ACL have nothing to declare;

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Figure legend

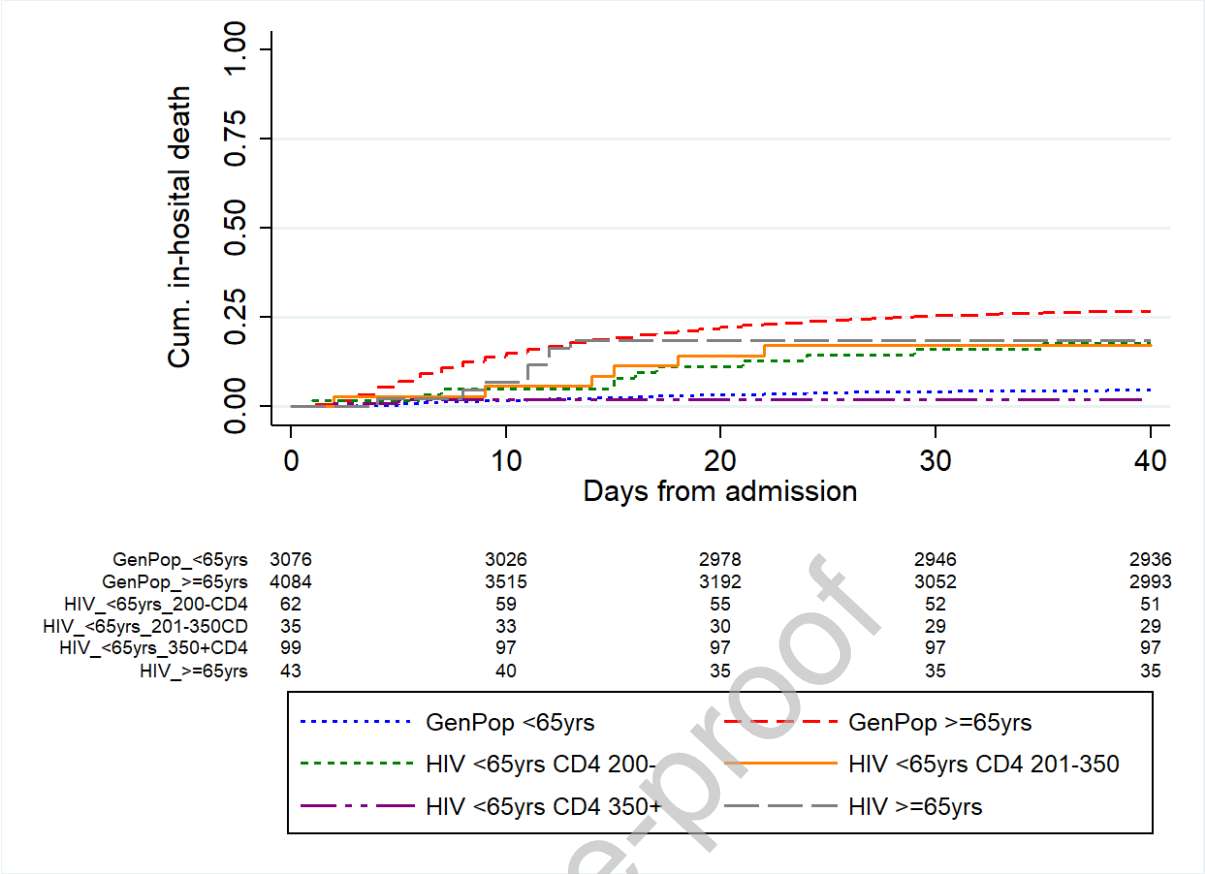

Figure 1. Kaplan-Meier curved of in-hospital mortality stratified by HIV status, age (≤65 vs >65 years) and CD4 cell count (≤200 vs >200-350 vs >350 cell/mm3).

		General Population		PLWH				
	Total	**<65 yrs**	**>=65 yrs**	**<65yrs CD4<= 200**	**<65yrs CD4 201-350**	**<65yrs CD4>350**	**>=65yrs**	**p**
	7,399 (100%)	**3,076 (41·6%)**	**4,084 (55·2%)**	**62 (0·8%)**	**35 (0·5%)**	**99 (1·3%)**	**43 (0·6%)**	
Age, median (IQR)	54 (68-80)	43 (52-58)	72 (79-85)	42 (50-57)	38 (49-58)	45 (53-59)	69 (72-77)	<0·001
Male sex at birth, n (%)	4493 (60·7)	2013 (65·4)	2293 (56·1)	46 (74·2)	31 (88·6)	74 (74·7)	36 (83·7)	<0·001
Ethnicity, n (%)								<0·001
Caucasian	6360 (86·0)	2269 (73·8)	3921 (96)	34 (54·8)	20 (57·1)	74 (74·8)	42 (97·7)	

Latinix	357 (4·8)	275 (8·9)	47 (1·2)	11 (17·7)	9 (25·7)	15 (15·2)	0 (0)	
Asian	294 (4·0)	257 (8·4)	33 (0·8)	1 (1·6)	2 (5·7)	1 (1)	0 (0)	
Black	82 (1·1)	42 (1·4)	13 (0·3)	15 (24·2)	4 (11·4)	7 (7·1)	1 (2·3)	
Maghreb/Arab	277 (3·7)	217 (7·1)	57 (1·4)	1 (1·6)	0 (0)	2 (2)	0 (0)	
Missing	29 (0·4)	16 (0·5)	13 (0·3)	0 (0)	0 (0)	0 (0)	0 (0)	
VOC period, n (%)								<0·001
WT/Alpha/Gamma (before 15Jun21)	4962 (67·1)	2249 (73·1)	2553 (62·5)	39 (62·9)	23 (65·7)	68 (68·7)	30 (699·8)	
Delta (15Jun21-19Dec21)	915 (12·4)	414 (13·5)	480 (11·8)	3 (4·8)	4 (11·4)	11 (11·1)	3 (7)	
Omicron (after 20Dec21)	1522 (20·6)	413 (13·4)	1051 (25·7)	20 (32·3)	8 (22·9)	20 (20·2)	10 (23·3)	
P/F at admission, median (IQR)	310 (239-379)	328 (265-395)	299 (220-357)	324 (255-467)	362 (309-429)	376 (300-514)	304 (202-381)	<0·001
missing	725 (99·8)	309 (10)	382 (99·3)	10 (16)	2 (5·7)	14 (14·1)	8 (18·6)	
P/F at admission (excluding missing) <300, n (%)	2938 (44)	1013 (36·6)	1858 (50·2)	21 (40·4)	8 (24·3)	21 (24·7)	17 (48·6)	<0·001
With pneumonia at admission (excluding missing), n (%)	5202 (85·3)	2094 (86·5)	3044 (85·3)	7 (41·2)	8 (64·5)	35 (62·5)	14 (58·3)	<0·001
missing	1300 (17·6)	655 (21·3)	516 (12·6)	45 (72·5)	22 (62·8)	43 (43·4)	19 (44·2)	
With pneumonia and/or P/F <300, n (%)	5612 (77·2)	2247 (75·1)	3257 (80·6)	23 (399·7)	16 (45·7)	46 (46·9)	23 (53·5)	<0·001
missing	132 (1·8)	86 (2·8)	41 (1)	4 (6·5)	0 (0)	1 (1)	0 (0)	
Comorbidities, n (%)								
Cerebro/cardiovascular disease	1103 (14·9)	117 (3·8)	969 (23·7)	0 (0)	4 (11·4)	5 (5·1)	8 (18·6)	<0·001
CKD	528 (7·1)	100 (3·3)	410 (10)	1 (1·6)	3 (8·6)	9 (99·1)	5 (11·6)	<0·001
Asthma	144 (1·9)	53 (1·7)	79 (1·9)	7 (11·3)	2 (5·7)	0 (0)	3 (7)	<0·001
Immune disorders/Autoimmune disorders	170 (2·3)	65 (2·1)	96 (2·4)	5 (8·1)	0 (0)	0 (0)	4 (9·9)	<0·001
Cancer	393 (5·3)	40 (1·3)	346 (8·5)	1 (1·6)	0 (0)	3 (3)	3 (7)	<0·001
Diabetes	637 (8·6)	165 (5·4)	440 (10·8)	13 (21)	4 (11·4)	8 (8·1)	7 (16·3)	<0·001
Liver Diseases (non ESLD)	998 (13·5)	262 (8·5)	708 (17·3)	3 (4·8)	2 (5·7)	14 (14·1)	9 (20·9)	<0·001
ESLD	48 (0·6)	10 (0·3)	31 (0·8)	2 (3·2)	4 (11·4)	1 (1)	0 (0)	<0·

								001
Hypertension	1744 (27·1)	290 (11·2)	1441 (38·6)	9 (15)	3 (99·4)	13 (13·7)	18 (42·9)	<0·001
COPD	165 (2·2)	52 (1·7)	95 (2·3)	7 (11·3)	5 (14·3)	4 (4)	2 (4·7)	<0·001
Lung Diseases (Asthma+COPD+Other Lung disease)	877 (11·8)	218 (7·1)	626 (15·3)	11 (17·7)	5 (14·3)	7 (7·1)	10 (23·3)	<0·001
Neurological Diseases	109 (2·8)	17 (1)	77 (4)	5 (8·5)	4 (13·3)	3 (3·5)	3 (7·9)	<0·001
Obesity, n (%)								<0·001
No	3706 (50·1)	1581 (51·4)	1946 (47·7)	54 (87·1)	25 (71·4)	71 (71·7)	29 (67·4)	
Yes	1296 (17·5)	633 (20·6)	630 (15·4)	4 (6·5)	5 (14·3)	17 (17·2)	7 (16·3)	
unknown	2397 (32·4)	862 (28)	1508 (36·9)	4 (6·5)	5 (14·3)	11 (11·1)	7 (16·3)	
Primary cycle COVID-19 vaccine complete, n (%)	1208 (16·3)	230 (7·5)	935 (22·9)	13 (21·0)	6 (17·1)	15 (15·1)	9 (20·9)	<0·001
missing	459 (6·2)	226 (7·3)	190 (4·6)	15 (24·2)	9 (25·7)	13 (13·1)	6 (13·9)	
Region, n (%)								<0·001
Lombardy	6144 (83)	2525 (82·1)	3530 (86·4)	18 (29)	12 (34·3)	45 (45·5)	14 (32·6)	
Lazio	995 (13·5)	498 (16·2)	409 (10)	28 (45·2)	17 (48·6)	32 (32·3)	11 (25·6)	
Emilia Romagna	121 (1·6)	26 (0·9)	79 (1·9)	2 (3·2)	1 (2·9)	9 (99·1)	4 (99·3)	
Sardinia	100 (1·4)	27 (0·9)	66 (1·6)	2 (3·2)	2 (5·7)	1 (1)	2 (4·7)	
Liguria	19 (0·3)	0 (0)	0 (0)	2 (3·2)	0 (0)	8 (8·1)	9 (20·9)	
Campania	10 (0·1)	0 (0)	0 (0)	4 (6·5)	2 (5·7)	3 (3)	1 (2·3)	
Marche	5 (0·1)	0 (0)	0 (0)	3 (4·8)	0 (0)	1 (1)	1 (2·3)	
Apulia	3 (0)	0 (0)	0 (0)	2 (3·2)	0 (0)	0 (0)	1 (2·3)	
Sicily	2 (0)	0 (0)	0 (0)	1 (1·6)	1 (2·9)	0 (0)	0 (0)	

Table 1. Characteristics of the study population according to age strata (< and ≥65 years) and for PLWH also CD4 cell count strata (≤200, 201-350 and >350)

List of abbreviations: GenPop, general population; PLWH, people living with HIV; n, number; IQR, Inter Quartile Range; VOC, variants of concern; WT, wilde type; P/F, PaO2/FiO2; CRP, C reactive protein; CKD, chronic kidney disease; ESLD, end stage liver disease9·

	PLWH n=239
CD4 count (cells/mm^3), median (IQR)	395 (161-620)

CD4 >350 (cells/mm^3), n (%)	125 (52·3)
CD4 201-350 (cells/mm^3), n (%)	44 (18·4)
CD4 ≤200 (cells/mm^3), n (%)	67 (30·2)
Months from CD4 count to hospitalization, medina (IQR)	1·2 (0·0-4·1)
HIV-RNA <50 copies/mL, n (%)	175 (76·1)
missing	9
Previous AIDS event, n (%)	78 (34·8%)
missing	16
Antiretroviral Regimes, n (%)	
2NRTIs+ INSTI	83 (34·7)
Dual INSTI based	30 (12·5)
2NRTIs + PI	21 (8·8)
2NRTIs + NNRTIs	31 (13)
Other regimens	42 (17·6)
missing or ART-naive	32 (13·4)

Table 2. Characteristics of PLWH.

List of abbreviations: PLWH, people living with HIV; n, number; IQR, Inter Quartile Range; NRTIs, nucleoside reverse transcriptase inhibitor; INSTI, Integrase strand transfer inhibitors; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; ART, antiretroviral treatment.

Overall*	**SHR**	**95% CI**	**aSHR**	**95% CI**
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6·83	5·75-8·11	1·79	1·39-2·31
PLWH ≥65 years	5·42	2·89-10·13	2·16	1·15-4·04
PLWH <65 years and CD4 cell count ≤200 cell/mm^3	5·08	3·01-8·57	9·69	5·50-17·07
PLWH <65 years and CD4 cell count 201-350 cell/mm^3	3·89	1·74-8·73	4·37	1·79-10·63
PLWH <65 years and CD4 cell count >350 cell/mm^3	0·86	0·32-2·32	1·11	0·41-2·99

Table 3. Unadjusted and adjusted Fine-Gray Cox regression model of the association between the 6 level's exposure and in-hospital mortality.

*Final model adjusted for age, sex at birth, ethnicity, region of enrolment, calendar period, immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, obesity and lung disease.

List of abbreviations: aSHR, adjusted Subdistribution Hazard Ratio; CI, confidence interval; PLWH, people living with HIV; GenPop, general population.

Restricted to subjects with pneumonia and/or P/F<300 at hospital admission*				
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6·28	5·26-7·51	1·78	1·37-2·32
PLWH ≥65 years	7·79	4·06-14·95	2·80	1·43-5·46
PLWH <65 years and CD4 cell count ≤200 cell/mm^3	7·41	3·97-13·83	9·83	4·75-20·35
PLWH <65 years and CD4 cell count 201-350 cell/mm^3	5·69	2·47-13·12	4·41	1·74-11·18
PLWH <65 years and CD4 cell count >350 cell/mm^3	0·86	0·32-2·32	1·23	0·38-3·95
Restricted to centers able to provide both HIV exposed an unexposed*				
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6·83	5·74-8·11	1·82	1·41-2·34
PLWH ≥65 years	4·00	1·48-10·78	1·75	0·64-4·75
PLWH <65 years and CD4 cell count ≤200 cell/mm^3	4·73	2·51-8·89	8·17	4·18-15·99
PLWH <65 years and CD4 cell count 201-350 cell/mm^3	3·95	1·62-9·62	5·45	2·29-13·00
PLWH <65 years and CD4 cell count >350 cell/mm^3	0·92	0·29-2·90	1·08	0·34-3·43
Overall^	SHR	95% CI	aSHR	95% CI
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6·83	5·75-8·11	1·86	1·44-2·39
PLWH ≥65 years	5·42	2·89-	2·18	1·18-

PLWH <65 years and CD4 cell count ≤200 cell/mm^3	5·08	10·13 3·01-8·57	8·65	4·06 4·91-15·22
PLWH <65 years and CD4 cell count 201-350 cell/mm^3	3·89	1·74-8·73	4·25	1·76-10·29
PLWH <65 years and CD4 cell count >350 cell/mm^3	0·86	0·32-2·32	1·04	0·39-2·78

Table 4. Unadjusted and adjusted Fine-Gray Cox regression model of the association between the 6 level's exposure and in-hospital mortality restricted to subjects with pneumonia and/or P/F<300 at hospital admission, restricted to centers able to provide both HIV exposed and unexposed and after rerunning the model by adjusting for comorbidities.

*Final model adjusted for adjusted for age, sex at birth, ethnicity, region of enrolment, calendar period, immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, neurologic disease obesity and lung disease

^ Final model adjusted for age, sex at birth, ethnicity, calendar period, region of enrolment and lung diseases

List of abbreviations: aSHR, adjusted Subdistribution Hazard Ratio; CI, confidence interval; PLWH, people living with HIV; GenPop, general population.

Declaration of Competing Interest

AGiacomelli reports speakers' honoraria for ViiV Healthcare and Gilead Sciences, advisor for Janssen-Cilag and Mylan; RG reports payments to her institution from Gilead Sciences, speakers' honoraria for ViiV Healthcare, Merck Sharp and Dohme and Gilead Sciences,

advisor for Thera Technologies, Janssen-Cilag and Gilead Sciences; GR reports consultancies/advisory from ViiV Helathcare, GSK, Merck Sharp and Dohme and Gilead Sciences; AGori received speaker's honoraria and feesfor attending advisory boards from ViiVHealthcare, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer and Novartis and received researchgrants from ViiV, Bristol-Myers Squibb, and Gilead; AM received speakers' honoraria from Gilead Sciences, and ViiV Healthcare, travel fee from Viiv Healthcare and participated in advisory boards sponsored by ViiV Healthcare; AV received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served an advisor for Janssen-Cilag; MM received speakers' honoraria from ViiV Healthcare; LT reports consultancies/advisory from Viiv Healthcare, Gilead Sciences and Janssen-Cilag and institutional fellowship from Gilead Sciences; GMarchetti participated to advisory boards of Gilead Sciences, ViiV Healthcare, Angelini and Janssen-Cilag, and received travel grants from ViiV-Healthcare and Janssen-Cilag; AdM participated in advisory board of Gilead Sciences, ViiV Healthcare, Merck Sharp and Dohme, Pfizer and GSK and reports research grant from Gilead Science, ViiV Healthcare, Merck Sharp and Dohme, GSK and Janssen-Cilag; AA received Research grants from Gilead Sciences, AstraZeneca, ViiV Healthcare and Honoraria from Gilead Science, AstraZeneca, GSK, Pfizer, Merck Sharp and Dohme, Moderna, Mylan, Janssen-Cilag, ViiV Healthcare; AT, SDB, SA, GMancarella, FMF, ADV, VM, MA and ACL have nothing to declare;