Original Research

Cytomegalovirus Seropositivity is Associated with Airflow Limitation in a Cohort of Veterans with a High Prevalence of Smoking

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Running Header: CMV seropositivity and airflow limitation

Author Conflict of Interest Statements
The authors report no conflicts of interest outside of the elsewhere-mentioned federal funding for the conduct of this study.

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Word Count: 2666

Keywords: COPD, viral infections, airflow limitation, cytomegalovirus, COPD outcomes
Abbreviations: COPD = Chronic obstructive pulmonary disease; AFL = Airflow limitation; CMV = Cytomegalovirus; FEV1 = Forced-expiratory-volume-in-1-second, FVC = Forced vital capacity, BMI = Body mass index, AECOPD = Acute exacerbations of COPD

Note: This article has an online supplement.
Abstract

Background

Cytomegalovirus represents an understudied chronic infection, usually contracted early in life, that causes chronic immune system alterations which can contribute to airflow limitations in a cohort of Veterans with a high prevalence of smoking. We studied 172 participants at-risk for and with airflow limitation with available cytomegalovirus serology to assess the relationship between cytomegalovirus infection and chronic obstructive pulmonary disease-related outcomes.

Methods

The study cohort includes 172 Veterans who are smokers with or at risk for the development of COPD. Clinical data were obtained by chart abstraction at enrollment. Cytomegalovirus affinity (ever-exposure) and avidity testing (length of exposure) were performed on plasma samples collected at enrollment. Bivariable and multivariable logistic regression was used to determine the relationship between both cytomegalovirus affinity and avidity and odds of prevalent airflow limitation (post-bronchodilator forced-expiratory-volume-in-1-s/forced vital capacity <0.70) at enrollment. In those with airflow limitation (n=84), bivariable and multivariable logistic regression was used to determine relationships between cytomegalovirus serostatus and reported exacerbations of COPD over two years prior to enrollment.

Results

Positive cytomegalovirus serostatus was independently associated with a 136% higher odds of airflow limitation (95% CI 1.11-5.06, P=0.03) at enrollment. Neither cytomegalovirus affinity nor avidity was associated with COPD exacerbations in the two years prior to enrollment.

Conclusion
Cytomegalovirus serostatus is independently associated with airflow limitation in a cohort of Veterans who smoke. Investigation into the timing of infection and alterations in cellular immunity caused by chronic cytomegalovirus infection and smoking related airways disease-related outcomes is warranted.

Abstract Word Count: 245
Introduction

The development of airflow limitation (AFL) in chronic obstructive pulmonary disease (COPD) is a hallmark of the condition. Although COPD is thought mainly to be due to exposure to noxious particles from combustible tobacco products or biomass fuels, altered innate and secondary immunity, extracellular matrix changes, workplace exposures, and genetic predisposition potentiate the effect of environmental exposures in the development of AFL.

The role of chronic herpesvirus infections, specifically cytomegalovirus (CMV), in the pathobiology and epidemiology of AFL is of particular interest due to the putative impact of chronic infections on immune cells and the paucity of clinical literature on this subject. CMV infections have been associated with all-cause mortality in persons who have AFL, but not associated directly with the development of AFL. Chronic CMV infection is thought to lead to a proliferation of T cell populations with an altered, pro-inflammatory activity which may synergize with environmental exposures to enhance deleterious effects. Understanding the associations between CMV+ serostatus, AFL prevalence, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) events will further elucidate relationships between CMV+ serostatus and presence of AFL in COPD.

To examine the relationship between CMV infection, AFL, and AECOPD, we studied a cohort of current and former smokers at the Cincinnati Veterans Affairs (VA) hospital with available spirometry testing and CMV serostatus and antibody avidity. We hypothesized that CMV+ serostatus and stronger CMV avidity (suggesting a longer-standing chronic infection and/or frequent CMV reactivation due to infectious or environmental insult) will be associated with
higher odds of prevalent AFL and increased historical AECOPD events in a cohort of Veterans who smoke.

Methods

Study Population

The study cohort was 172 current and former smokers recruited from the Cincinnati Veterans Affairs Hospital system in Cincinnati, Ohio and included 84 participants with and 88 without [defined as a post-bronchodilator forced-expiratory-volume-in-1-second (FEV1)/forced vital capacity (FVC) ratio <0.70] AFL who had stored blood samples for CMV serology. Participants were recruited from the pulmonary clinic and were included if their reason for referral was listed as ‘COPD’, ‘chronic bronchitis’, ‘emphysema’, or were thought to be at risk due to the presence of respiratory symptoms and smoking without the presence of another chronic lung disease. Only those with a smoking history (never smokers with the abovementioned referral diagnoses have been excluded), available PFTs, and no other underlying lung disease were included in the study. Study procedures were performed after obtaining written informed consent from patients. The study design was reviewed and approved by the VA Research and Development Committee and the University of Cincinnati Institutional Review Board (IRB# 2014-2354). All methods were performed in accordance with the relevant guidelines and regulations. Data from patients, such as questionnaires, spirometry results, and all specimens were assigned a unique study number to de-identify patient personal information.

Data Collection
Demographic data (age, gender, race), body mass index (BMI), inhaled medication usage, smoking status, and pack-years smoked were collected at enrollment. BMI was categorized by American Association of Clinical Endocrinologists/American College of Endocrinology guidelines: underweight (<18.5 kg/m2), normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obesity class I (30-34.9 kg/m2), and obesity class II-III (>35 kg/m2). Pre- and post-bronchodilator spirometry was performed at the time of enrollment according to American Thoracic Society/European Respiratory Society guidelines. COPD was defined as a participant with a history of smoking who had AFL as defined above. AECOPD was determined by review of each patient’s VA medical records in the two years prior to enrollment. Exacerbations were collected over the two years prior to enrollment and classified by the total number of AECOPD and AECOPD severity: moderate (worsening of baseline COPD symptoms requiring escalation of therapy but not hospitalization) and severe (worsening of COPD symptoms requiring hospitalization or emergency department care). Plasma samples were collected at enrollment and isolated from lithium heparin anticoagulated blood and stored at -80°C until use. Assays to assess the presence and antigen-binding activity of CMV antibodies were performed by ELISA according to the manufacturer’s protocol (VIDITEST anti-CMV IgG and IgG avidity, Vidia, Czechoslovakia). The avidity of CMV antigen binding, which measures the strength which CMV-directed IgG binds to CMV epitopes which starts weak and becomes stronger up to six months after initial infection was also performed. High avidity represents long-standing infection, repeat CMV exposure, or frequent CMV reactivation from environmental or infectious exposure, while low represents a more recent CMV infection (roughly within the prior six months).
Statistical analysis

Descriptive statistics were used to examine the mean with standard deviation (normal distribution) or median with Q1-Q3 ranges (non-normal distribution) for continuous variables and frequency and percentage for categorical variables in the entire cohort. Participants were dichotomized based on a positive CMV affinity test (CMV+) vs. negative (CMV-) test. Two-sample Student’s t-test or Mann-Whitney U testing and chi-squared testing were used to determine the relationships between CMV serostatus and continuous and categorical variables, respectively. Bivariable and multivariable logistic regression analyses were used to assess the relationships between CMV serostatus (exposure) and AFL (outcome). In multivariable models, covariables were selected based on clinical relevance and include age (per 5 years), black race, female gender, pack-years smoked (per 5 years), and BMI classification. The associations between CMV avidity (high as referent; exposure) and AFL (outcome) were assessed by bivariate and multivariable analyses. For multivariable analysis, the same variables were used as above. Sensitivity analyses were performed in statistically significant models using BMI as a continuous rather than categorical variable.

We also assessed the associations between the outcome of medical chart documented AECOPD events in the two years prior to enrollment and CMV status in participants with AFL (n=84). AECOPD was modeled as either no AECOPD (0 events) or AECOPD (1+ event) or total number of exacerbations over the two years of retrospective data collection. AECOPD events were classified as total, moderate, or severe severity in each analysis based on the criteria above. Bivariable and multivariable logistic regression was used to model AECOPD as no events over the prior two years (0) vs. or one-or-more events over the prior two years (1+) and Poisson
regression was used to model AECOPD events as counts (number of exacerbations over two years prior to enrollment). Multivariable models included the covariables of age, black race, female sex, pack-years smoked, current smoking, BMI classification, and post-bronchodilator FEV1. Due to the high number of participants reporting no exacerbations in the cohort, zero-inflated negative binomial regression was also used to assess the associations between the number of AECOPD and CMV status.

Results

Description of Cohort

In the overall cohort, 49% of participants were CMV+ (Table 1), 87% of whom had either high or intermediate avidity tests suggesting long-standing and/or repeat CMV exposure. Females composed 6% of the cohort and 24% reported black race. The mean BMI was 27 kg/m² and 36% reported inhaled corticosteroid use. Mean post-bronchodilator FEV1 was 74%-predicted and FEV1/FVC was 0.71. Post-bronchodilator AFL was present in 49% of the cohort.

In those with AFL/COPD, 52% reported at least one AECOPD in the last two years. The median exacerbation count for those with AFL/COPD (n=84) was 1, with a Q1-Q3 of 0-2, and a range of 0-9 AECOPD events.

CMV+ participants were significantly older (63 vs. 60 years-old). There was no difference in BMI, current vs. former smoker, and pack years smoked between the two groups. There were no There was no difference in pre- or post-bronchodilator FEV1 %predicted between the two
groups. There was no association between CMV+ serostatus and exacerbators vs. non-exacerbators (Table 2), type of AECOPD events, or number of AECOPD events.

**Associations between CMV status and AFL**

In bivariable logistic regression analysis, CMV+ participants had 112% (OR 2.12) higher odds of having AFL (95% CI 1.15-3.88, P=0.002). In multivariable regression controlling for clinically relevant covariables, CMV+ participants had 136% (OR 2.36) higher odds of AFL (95% CI 1.11-5.06, P=0.01) (Table 3). There were no statistically significant relationships between CMV avidity in bivariate or multivariable analysis. In bivariate regression, neither high binding avidity [OR 3.90 (95% CI 0.76-20.0); P=0.12] nor intermediate binding avidity [OR 2.00 (95% CI 0.51-7.88); P=0.32] were associated with AFL. In multivariable regression using the same covariables as above, neither high binding avidity [OR 5.74 (95% CI 0.76-27.0); P=0.07] nor intermediate binding avidity [OR 4.53 (95% CI 0.67-49.5); P=0.11] were associated with AFL.

**Associations between CMV Status and AECOPD**

In cohort participants with AFL/COPD (n=84), the association between CMV status and AECOPD and odds and incidence rates were assessed. In bivariable analysis, there were no associations between odds of having 1+ vs. 0 of any AECOPD type, moderate AECOPD, or severe AECOPD and CMV+ serostatus. No significant associations were seen in multivariable logistic regression modeling and the results are presented in Supplementary Table 1.

With AECOPD events modeled as counts in Poisson regression, CMV+ status was associated with a lower incidence of total AECOPD [IRR 0.68 (95% CI 0.46-0.98), P=0.04] and moderate
AECOPD [IRR 0.63 (95% CI 0.40-0.98); P=0.04], but no relationship was seen with severe AECOPD. The relationships between lower incidence rate and CMV+ status were attenuated in multivariable models controlling for clinically relevant covariates (Supplementary Table 2). When modeling as counts using zero-inflated negative binomial regression, there were no significant associations observed in bivariate or multivariable analyses between CMV+ status and AECOPD outcomes.

Discussion

In this study of 172 persons at risk for AFL, the presence of serum antibodies to CMV was independently associated with increased odds of AFL when controlled for clinically relevant covariates, including demographic variables, pack-years smoked, and BMI. These findings suggest a remote CMV exposure and potential episodes of acute illness leading to CMV reactivation may be associated with prevalent AFL in a cohort of Veterans with a high prevalence of smoking. In participants with AFL, there was no correlation between CMV+ status and increased odds or incidence of reported AECOPD in the two years prior to enrollment when controlled for clinically relevant covariates.

To date, limited information exists in the literature regarding chronic CMV infection and associations with obstructive lung disease. Ours is the largest cohort to-date looking specifically at epidemiologic associations between CMV serostatus and airflow-related outcomes, as well as leveraging CMV antibody avidity to approximate timing of CMV exposure. Another study used proportional hazard modeling to associate CMV infection with COPD-related mortality in both those with and without AFL at the time of enrollment. These findings are notable in light of...
other studies associating chronic CMV infection and all-cause mortality that was believed to be due to chronic low-grade inflammation.\textsuperscript{8} It has been proposed that this pro-inflammatory state may be driven by proliferation of CD28- T cells caused by continual CMV reactivation in those with chronic airways disease.\textsuperscript{9} Our findings further this putative relationship by describing the independent association between CMV+ serostatus and prevalent spirometry-defined AFL in a clinical cohort of 199 Veterans with a high prevalence of smoking for the development of COPD. Also, assessment of CMV IgG antibody avidity and relationships with COPD in CMV+ participants show that those with low avidity (suggesting more recent CMV infection compared to longer standing infections with more reactivations) have a marginally significant 77% lower odds of having AFL in our cohort, as well. While we cannot completely discern if CMV infection is on the causal pathway to AFL development, these findings suggest a potential relationship between CMV infection and/or frequent CMV reactivations and either the development of airways obstruction or failure to reach full potential lung function due to CMV infection early in life (the timing of which we cannot infer in this analysis).

CMV is rarely cleared after initial infection and can cause a latent, subclinical chronic infection which may promote a pro-inflammatory state with a wide range of adverse consequences.\textsuperscript{17-20} The effect of CMV serostatus on atherosclerosis development is a well-studied example of a relationship between CMV serostatus and long term health outcomes as atherosclerosis and smoking-related lung diseases are thought to be pathophysiologically related. Chronic CMV infection is associated with increased levels of inflammatory cytokines associated with the progression of atherosclerosis\textsuperscript{21,22} with potential associations between CMV-positivity and clinical atherosclerotic outcomes.\textsuperscript{22} More advanced airways obstruction\textsuperscript{23}, increased
inflammatory markers in those with COPD \textsuperscript{24}, and increased products of extracellular matrix breakdown\textsuperscript{25} are all associated with worse atherosclerosis-related outcomes. The presence of CD28\textsuperscript{−} T-cells seems to play a role in the putative link between CMV infection and poor cardiovascular and pulmonary outcomes.\textsuperscript{18,26} Similar cellular pathways to adverse clinical events in COPD and atherosclerosis, along with the strong implication of a link between inflammation-driven pathophysiology in these diseases, lend credence to the potential for chronic CMV infection to promote systemic inflammation that may cause airways disease in at-risk individuals. Longitudinal studies, preferentially observing lung function decline over several years, exacerbation frequency and severity, and outcomes in comorbid conditions in smokers or COPD patients with CMV exposure will add further clarity to this hypothesis.

Future studies should focus on the timing of initial CMV infection or focus on subjects at-risk for COPD in adolescence or early mid-life. Generally, chronic airways obstruction is thought to be due to either failure of the lungs to reach maximal capacity due to a variety of early-life factors and/or a more rapid decline in lung function after full lung development.\textsuperscript{27,28} In immunocompetent individuals infected with CMV, manifestations tend to be subclinical but the presence of the virus elicits continued immune surveillance.\textsuperscript{29} The presence of CMV may alter particular immune cell structure and function which may potentiate and augment the inflammatory response to noxious stimulants subsequently leading to AFL/COPD. Natural Killer (NK) cells are indispensable in the control of CMV infections.\textsuperscript{30} In the presence of a chronic CMV infection, NK cells have a subtype shift to more cytotoxic and pro-inflammatory entities with an increase in CD57 and NKG2C signaling properties.\textsuperscript{31-34} A shift to NK cell populations expressing this signaling has been associated with AECOPD previously\textsuperscript{31}, and further
understanding the long term effects of expressing these NK cell populations in the development of AFL is an important, ongoing endeavor. Due to the need for constant immune control, persons with CMV infection also have alterations of their T-cell population that may, over time, exhaust the T-cell response leading to early immunoscenescence.\textsuperscript{29,35-37} This mechanism may put active smokers at higher risk of lung function decline. Also, childhood CMV infection potentially may interdict full lung maturation increasing the subsequent risk of AFL should these individuals be exposed to tobacco smoke or other noxious inhalants. CMV infection in early adulthood is associated with relative poverty\textsuperscript{36}, an already known risk factor for COPD risk as an adult.\textsuperscript{38} Our findings raise potential questions about the potential role of CMV infections, the subsequent development of AFL, and whether this association more specifically affects children from a low socioeconomic status or represents CMV infection contracted at other life stages. Further study specifically focusing on associations between early and mid-life CMV+ serostatus and maximum lung growth and lung function decline is warranted.

This study has limitations. This study is cross-sectional and, as such, we are only able to show CMV+ serostatus and increased odds of COPD prevalence. Due to the high number of those with AFL we cannot approximate true risk. While this finding is novel, further longitudinal study is needed to more thoroughly assess this relationship. Further, the CMV infected cohort was older, more likely to smoke, and had worse lung function potentially putting these participants at a higher risk of developing a CMV infection rather than a CMV infection being the cause of these findings. Due to these samples being collected in the Veterans’ Administration health system, females are under-represented which limits generalizability. Further, using a VA-based cohort may limit generalizability to the overall population. Collection of socioeconomic status would
have improved the modeling approach based on associations between poverty, CMV status, and COPD as discussed above. The reported AECOPD odds were determined from events only measured in the VA medical record and non-VA COPD-related healthcare encounters were not recorded and AECOPDs may have been undercounted. The relatively small sample size may impact our ability to assess some associations due to the effect on statistical power, namely the relationship between avidity and AFL. Also, the use of historical AECOPD events raises the possibility of survivorship bias, which would influence our reported associations.

Conclusion

In conclusion, in a sample of Veterans who smoke, CMV+ serostatus is associated with an increased odds of AFL when controlled for clinically relevant cofactors. Based upon these findings, longitudinal studies of associations between early- and mid-life CMV exposure and lung function decline in smokers will better elucidate this proposed relationship. Investigation of factors mitigating early- and mid-life CMV exposures and increased risk of the development of AFL would prove beneficial, but remain theoretical at the time of this writing.

Abbreviations

CMV=cytomegalovirus; BMI=body mass index; ICS=inhaled corticosteroid; FEV1=forced-expiratory-volume-in-1-second; FVC=forced vital capacity; COPD=chronic obstructive pulmonary disease; AFL=airflow limitation; AECOPD=acute exacerbations of COPD

Ethical Approval and Consent to Participate
The study design was reviewed and approved by the VA Research and Development Committee and the University of Cincinnati Institutional Review Board (IRB# 2014-2354). All authors agreed to submission of the final, submitted manuscript.

Availability of Data and Materials
Data for this study are from a deidentified cohort. Data sets for this article are stored in the Borchers Lab at the University of Cincinnati and are available by contacting Dr. Borchers at borchert@ucmail.uc.edu.

Declaration of Interest
RMB, AO, LL, TH have no competing interests. MTB receives grants from the NIH and VA. RJP is a site PI on NIH funded studies and recently on a clinical trial funded by Sanofi.

Acknowledgements
RMB wrote the manuscript which was critically assessed and edited by all other authors. MTB, AO, TH, LL, and RJP collected the data. RMB performed the statistical analysis. All authors were involved in the conceptualization of the manuscript.
References


Table 1. Description of cohort of 199 participants.

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<th></th>
<th>Total</th>
<th>CMV-</th>
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<tbody>
<tr>
<td>n</td>
<td>172</td>
<td>88</td>
<td>84</td>
<td></td>
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<td>Age, years, mean(SD)</td>
<td>61 (9.0)</td>
<td>59.9 (9.5)</td>
<td>62.7 (9.0)</td>
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<td>Female</td>
<td>10 (5.8)</td>
<td>7 (8.0)</td>
<td>3 (3.6)</td>
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<tr>
<td>Black Race</td>
<td>41 (23.8)</td>
<td>20 (22.7)</td>
<td>21 (25.0)</td>
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<td>BMI, kg/m², mean(SD)</td>
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<td>28.1 (5.87)</td>
<td>27.0 (4.08)</td>
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<tr>
<td>ICS Use</td>
<td>43 (35.8)</td>
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<td>BMI Class, n(%)</td>
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</tr>
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<td>Obesity 2-3</td>
<td>13 (76)</td>
<td>11 (12.5)</td>
<td>2 (38)</td>
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<td>19 (2.0)</td>
<td>16 (37)</td>
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<td>66 (38.4)</td>
<td>27 (30.7)</td>
<td>3 (46.4)</td>
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<td>Normal</td>
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<td>226 (31.0)</td>
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<td>3 (1.7)</td>
<td>2 (2.3)</td>
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<td>Current</td>
<td>100 (58.4)</td>
<td>47 (53.4)</td>
<td>53 (63.1)</td>
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<td>Pack-years</td>
<td>41.5 (22.6-58.25)</td>
<td>41 (20-54.5)</td>
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<tr>
<td>Pre-Bronchodilator</td>
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<td></td>
</tr>
<tr>
<td>FEV1, L, mean(SD)</td>
<td>2.36 (0.93)</td>
<td>2.34 (0.90)</td>
<td>2.17 (0.96)</td>
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<td>FEV1, %-predicted,</td>
<td>69 (25)</td>
<td>69.2 (24.9)</td>
<td>65.9 (25.7)</td>
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<td>mean(SD)</td>
<td>3.24 (1.03)</td>
<td>3.44 (1.01)</td>
<td>3.25 (1.04)</td>
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<tr>
<td>FVC, L, mean(SD)</td>
<td>0.71 (0.56-0.79)</td>
<td>0.73 (0.58-0.8279)</td>
<td>0.67 (0.56-0.78)</td>
<td>0.22</td>
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<tr>
<td>FEV1/FVC</td>
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<td></td>
<td></td>
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<tr>
<td>Post-Bronchodilator</td>
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<td></td>
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<td></td>
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<tr>
<td>FEV1, L, mean(SD)</td>
<td>2.46 (0.94)</td>
<td>2.49 (0.90)</td>
<td>2.28 (0.97)</td>
<td>0.15</td>
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<tr>
<td>FEV1, %-predicted,</td>
<td>74.4 (25.4)</td>
<td>76.973.6 (25.1)</td>
<td>69.5 (25.8)</td>
<td>0.29</td>
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<tr>
<td>mean(SD)</td>
<td>3.41 (1.03)</td>
<td>3.60 (1.02)</td>
<td>3.43 (1.03)</td>
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<td>0.71 (0.57-0.80)</td>
<td>0.75 (0.61-0.81)</td>
<td>0.67 (0.56-0.80)</td>
<td>0.15</td>
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<tr>
<td>FEV1/FVC</td>
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<tr>
<td>Airflow Limitation/COPD</td>
<td>84 (49)</td>
<td>35 (39.8)</td>
<td>49 (58.3)</td>
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<td></td>
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<tr>
<td>Total</td>
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<td>1 (0-2)</td>
<td>1 (0-2)</td>
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<td>1 (0-2)</td>
<td>0 (0-1)</td>
<td>0.43</td>
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<td>Severe</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0.43</td>
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<td>Exacerbations*, Any vs None</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44 (52.3)</td>
<td>19 (54.3)</td>
<td>25 (51.0)</td>
<td>0.77</td>
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<tr>
<td>Moderate</td>
<td>41 (48.1)</td>
<td>18 (51.4)</td>
<td>23 (46.9)</td>
<td>0.69</td>
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<td>Severe</td>
<td>18 (21.4)</td>
<td>9 (25.7)</td>
<td>9 (18.37)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

All outcomes are n(%) or median (Q1-Q3) unless otherwise noted.

Abbreviations: CMV=cytomegalovirus; BMI=body mass index; ICS=inhaled corticosteroid; FEV1=forced-expiratory-volume-in-1-second; FVC=forced vital capacity; COPD=chronic obstructive pulmonary disease.
*Exacerbations collected via review of medical records over the two years prior to enrollment and include only participants with COPD (n=84)

<table>
<thead>
<tr>
<th>Table 2. Participants with any chart-reported acute exacerbations of COPD in the two years prior to enrollment by CMV serostatus*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>CMV +</td>
</tr>
<tr>
<td>CMV -</td>
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</table>

Abbreviations: COPD = Chronic obstructive pulmonary disease; CMV = Cytomegalovirus

*84 participants with spirometry-confirmed COPD are included in this table

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<thead>
<tr>
<th>Table 3. Multivariable logistic regression* describing the association between CMV+ status and spirometry-confirmed COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR=odds ratio; CMV=cytomegalovirus; BMI=body mass index
### Supplemental Tables

#### Supplemental Table 1. Multivariable logistic regression* describing associations between CMV+ status and AECOPD outcomes over the two years prior to enrollment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Exacerbations</td>
<td>0.89 (0.31-2.50)</td>
<td>0.81</td>
</tr>
<tr>
<td>Moderate Exacerbations</td>
<td>0.68 (0.21-2.26)</td>
<td>0.53</td>
</tr>
<tr>
<td>Severe Exacerbations</td>
<td>0.94 (0.33-2.65)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Controlled for age, race, gender, smoking status, pack-years smoked, BMI, and pre-bronchodilator FEV1.

ORs represent the odds ratios of given AECOPD type for CMV+ vs. CMV-

Abbreviations: CMV=cytomegalovirus; AECOPD=acute exacerbations of chronic obstructive pulmonary disease; OR=odds ratio; BMI=body mass index; FEV1=forced-expiratory-volume-in-1-second

#### Supplemental Table 2. Multivariable Poisson regression* describing associations between CMV+ status and AECOPD outcomes over the two years prior to enrollment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IRR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Exacerbations</td>
<td>0.82 (0.54-1.23)</td>
<td>0.34</td>
</tr>
<tr>
<td>Moderate Exacerbations</td>
<td>0.82 (0.50-1.34)</td>
<td>0.43</td>
</tr>
<tr>
<td>Severe Exacerbations</td>
<td>0.84 (0.39-1.80)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*Controlled for age, race, gender, smoking status, pack-years smoked, BMI, and pre-bronchodilator FEV1.

IRRs represent the incidence rate ratios of given AECOPD type for CMV+ vs. CMV-

Abbreviations: CMV=cytomegalovirus; AECOPD=acute exacerbations of chronic obstructive pulmonary disease; IRR=incidence rate ratio; BMI=body mass index; FEV1=forced-expiratory-volume-in-1-second