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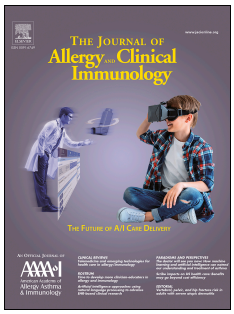

Immunologic resilience and COVID-19 survival advantage

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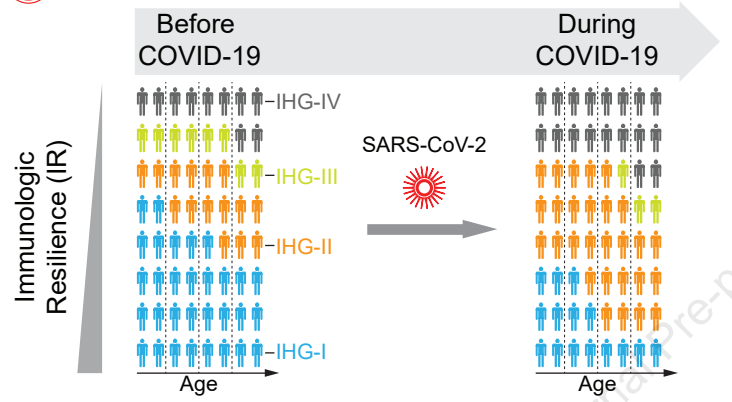
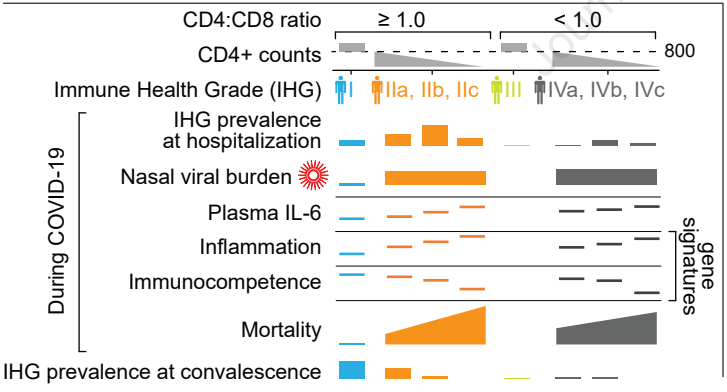
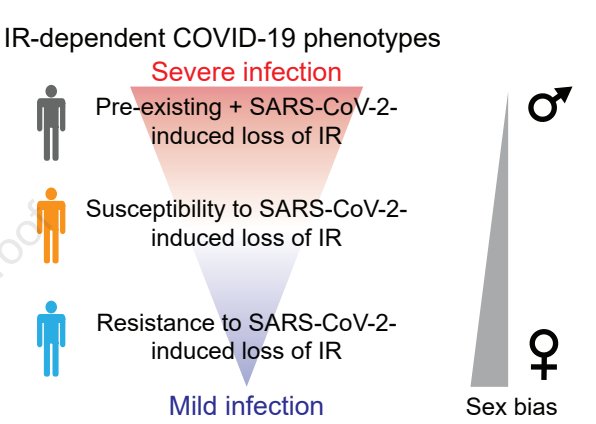
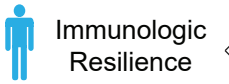
Immunologic resilience (IR)-dependent COVID-19 phenotypes (independent of age)









Mechanisms

- ↑ Immunocompetence
- ↓ Inflammation

Outcomes

- ↓ COVID-19 severity / mortality
  Prospective COVID-19 cohort
  n = 522
- ↑ Lifespan in general population
  Framingham Heart Study
  n = 2,306

Immunologic resilience and COVID-19 survival advantage

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Abstract

Background: The risk of severe COVID-19 varies significantly among persons of similar age and is higher in males. Age-independent, sex-biased differences in susceptibility to severe COVID-19 may be ascribable to deficits in a sexually dimorphic protective attribute that we termed immunologic resilience (IR).

Objective: To examine whether deficits in IR that antedate or are induced by SARS-CoV-2 infection independently predict COVID-19 mortality.

Methods: IR levels were quantified with two novel metrics: immune health grades (IHG-I [best] to IHG-IV) to gauge CD8+ and CD4+ T-cell count equilibrium, and blood gene expression signatures. IR metrics were examined in a prospective COVID-19 cohort (*n*=522); primary outcome was 30-day mortality. Associations of IR metrics with outcomes in non-COVID-19 cohorts (*n*=13,461) provided the framework for linking pre-COVID-19 IR status to IR during COVID-19, as well as to clinical outcomes.

Results: IHG-I, tracking high-grade equilibrium between CD8+ and CD4+ T-cell counts, was the most common grade (73%) among healthy adults, particularly in females. SARS-CoV-2 infection associated with underrepresentation of IHG-I (21%) vs. overrepresentation (77%) of IHG-II or IHG-IV, especially in males vs. females ($P<0.01$). Presentation with IHG-I associated with 88% lower mortality, after controlling for age and sex; reduced risk of hospitalization and respiratory failure; lower plasma IL-6 levels; rapid clearance of nasopharyngeal SARS-CoV-2 burden; and gene expression signatures correlating with survival that signify immunocompetence and controlled inflammation. In non-COVID-19 cohorts, IR-preserving metrics associated with resistance to progressive

influenza or HIV infection, as well as lower 9-year mortality in the Framingham Heart Study, especially in females.

Conclusion: Preservation of immunocompetence with controlled inflammation during antigenic challenges is a hallmark of IR and associates with longevity and AIDS resistance. Independent of age, a male-biased proclivity to degrade IR before and/or during SARS-CoV-2 infection predisposes to severe COVID-19.

Clinical implications: Biomarkers tracking immunologic resilience may have broad prognostic utility, as they associated with longevity, as well as resistance to a progressive disease course during SARS-CoV-2, influenza, or HIV infection.

Capsule summary: Irrespective of age, severe COVID-19 is more likely in persons with pre-existing or SARS-CoV-2-induced deficiency in immunologic resilience, an attribute linked to higher immunocompetence and lower inflammation. This readily trackable deficiency, more prevalent in males, also associated with shorter lifespan.

Keywords: Aging, Biomarkers, COVID-19, HIV, Immune, Inflammation, Influenza, SARS-CoV-2.

Abbreviations

AIDS, acquired immunodeficiency syndrome

ART, antiretroviral therapy

CMV, cytomegalovirus

COVID-19, coronavirus disease-2019

FHS, Framingham Heart Study

GO-BP, gene ontology-biological process

H-S, hospital survivors

HIV, human immunodeficiency virus

HR, hazard ratio

IC, immunocompetence

IF, inflammation

IFN, interferon

IHG, immune health grade

IMM-AGE, immune age

IQR, interquartile range

IR, immunologic resilience

MHC, Major histocompatibility complex

N, viral nucleoprotein

NH-S, nonhospitalized survivors

159 NS, nonsurvivors

160 OR, odds ratio

161 RR, rate ratio

162 SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

163 SLE, systemic lupus erythematosus

164 STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

Introduction

Despite significant progress in the identification of host factors that influence COVID-19 outcomes[1-7], the reasons why persons of similar ages vary in their susceptibility to developing progressive COVID-19, characterized by hospitalization, respiratory failure, and death, are unclear. We sought to identify persons with this susceptibility through the articulation of a parsimonious basis for three conundrums. First, while the risk of progressive COVID-19 increases with age, some older persons resist progression, manifesting asymptomatic or mild (i.e., nonprogressive) COVID-19[1, 2], whereas, some younger persons manifest progressive COVID-19[3, 4]. Second, females appear to resist progressive COVID-19 more effectively than males[5, 6, 8, 9]. This resistance aligns with evidence that females often manifest features of superior immunocompetence (resistance to some infections, longevity[10-17]). Third, clearance rates of nasopharyngeal SARS-CoV-2 vary, with delays contributing to progressive COVID-19[18, 19].

We reasoned that a parsimonious basis for these conundrums is that, among persons of similar ages, progressive COVID-19 is ascribable to a deficit in a sexually dimorphic, immunity-optimizing attribute that antedates infection or is induced by SARS-CoV-2 infection. We termed this attribute as immunologic resilience (IR), defined as the capacity to preserve or restore immunocompetence and control inflammation in the face of antigenic challenges experienced throughout life. Thus, we posited that maintenance of a state of higher immunocompetence (IC) and lower inflammation (IF; IC^{high}-IF^{low}) constitutively and/or during antigenic exposures is the hallmark of IR.

In this context, we hypothesized that individuals of similar ages may differ in their capacity to preserve IR before and during COVID-19, defining three major IR-dependent COVID-19 phenotypes (**Table 1**). In SARS-CoV-2-negative persons, a deficit in IR is characterized by an immunosuppressive, pro-inflammatory state (IC^{low}-IF^{high}) that is more common in males and predisposes to a shorter lifespan, as well as a progressive disease course during viral infections, such as influenza and HIV. If such persons acquire SARS-CoV-2 infection, the pre-existing deficit in IR may increase susceptibility to development of progressive COVID-19 as well as amplify SARS-CoV-2-induced deficits in IR (phenotype 3; **Table 1**). In contrast, resistance to developing deficits in IR before and during SARS-CoV-2 infection associates with nonprogressive COVID-19 (phenotype 1; **Table 1**). Thus, persons with the IR-dependent COVID-19 phenotype 3 may manifest two distinct IC^{low}-IF^{high} states: one antedating infection and one induced by SARS-CoV-2.

To test our hypothesis, we developed novel laboratory (lymphocyte level-based) and transcriptomic (gene expression-based) metrics of IR. We juxtaposed the distributions and associations of IR metrics in a prospective COVID-19 cohort with those in cohorts of SARS-CoV-2-negative persons. This juxtaposition provided empiric evidence in support of three IR-dependent COVID-19 phenotypes (**Table 1**). Additionally, we evaluated the utility of IR metrics in the early prediction of all-cause 30-day COVID-19 mortality, the primary outcome of this study. We also examined secondary outcomes that track clinical indicators (e.g., hospitalization, hospital length-of-stay) and biomarkers (e.g., plasma IL-6 and nasopharyngeal SARS-CoV-2 levels) of progressive COVID-19.

Methods

Study Design

Cohort details and analytical plan are in the Supplementary materials. A prospective observational cohort of 522 SARS-CoV-2-positive adults was evaluated at the South Texas Veterans Health Care System (STVHCS) from March 20 to October 15, 2020 (cohort features in **Figure E1A, Table 2,** and **Table E1**). Hospitalized and nonhospitalized patients were included, and a subset was studied through to the convalescence phase of the infection. The distribution patterns of IR metrics and their associations with outcomes in non-COVID-19 cohorts provided the framework for understanding the contributions of pre-COVID-19 IR status to COVID-19 outcomes. We evaluated previously well-characterized non-COVID-19 cohorts of persons exposed to four types of antigenic stimulation: (i) varied causes across lifespan (four cohorts; total *n*=8,201), including the community-based SardiNIA aging cohort (*n*=3,896;[20]) and the Offspring cohort of the Framingham Heart Study (FHS; *n*=2,306;[21]); (ii) acute influenza infection (influenza virus challenge cohort of younger adults[22] and two adult cohorts of natural infection[23, 24]; total *n*=218); (iii) self-antigen-associated antigenic stimulation in younger adults with systemic lupus erythematosus (SLE)[25] (*n*=53); and (iv) chronic HIV infection in the adult HIV Natural History Study[26-30] (*n*=4,883) (**Tables E2, E3**). Healthcare workers at STVHCS with risk of exposure to SARS-CoV-2 were also evaluated (*n*=34).

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies (STROBE Table in supplement)[31]. This study was approved by the University of Texas Health Science

Center at San Antonio, Texas, Institutional Review Board. All authors vouch for the completeness of the data and adherence to the analytic plan articulated *a priori* (Supplementary methods, **Figure E1B**).

Procedures

Clinical and laboratory assessments (e.g., scores of a clinical ordinal scale[32], CD4+ and CD8+ T-cell counts, and plasma IL-6 levels) were recorded (Supplementary methods). These assessments were evaluated at baseline (presentation to the hospital or home visit) as well as prospectively (daily) during hospitalization and at least once in the convalescence phase. Cytomegalovirus (CMV) serostatus was evaluated at baseline. RNA from nasal cells collected from hospitalized patients was sequenced (RNA-Seq) to quantify SARS-CoV-2 levels as well as identify human genes whose expression levels were associated with SARS-CoV-2 levels and survival (Supplementary methods). RNA from peripheral blood cells was also sequenced.

Definitions and outcomes

Progressive COVID-19 was defined as progression along the continuum from hospitalization to need for any respiratory support and/or death. The primary outcome was all-cause 30-day COVID-19 mortality. Secondary outcomes included: hospitalization, requirement of any respiratory support or mechanical ventilation; progression quantified by an increase in an 8-category clinical ordinal scale (supplementary methods); hospital length-of-stay (recovery rate); all-cause 120-day mortality; plasma IL-6 levels (biomarker of inflammation and mortality[33-37]); and nasal SARS-CoV-2 clearance, defined as time to

achievement of <10 counts of the viral nucleoprotein (*N*) gene. Clinical indicators of nonprogressive vs. progressive COVID-19 disease course were nonhospitalized vs. hospitalized patients, as well as survivors vs. nonsurvivors within 120 days of presentation. Prespecified outcomes in the non-COVID-19 cohorts were all-cause age-adjusted mortality over 9 years in the FHS, severity of influenza infection, and hazard of AIDS. A lower hazard of mortality in the COVID-19 cohort or FHS was defined as a survival advantage.

Measurements/Predictors: Metrics of Immunologic Resilience

To capture the cellular and molecular events that may associate with IR status, we derived laboratory and transcriptomic metrics of IR, which served as predictors in this study. Laboratory metrics of IR, termed immune health grades (IHGs), were derived on the principles that: (i) IR tracks superior immunocompetence, (ii) peripheral blood CD8+ and CD4+ T-cell levels influence immunity, and (iii) CD4+ lymphopenia is a characteristic of aging, SLE, and HIV infection[38-51]. We posited that the level of equilibrium vs. disequilibrium between peripheral blood CD8+ and CD4+ T-cells, rather than their absolute values, may be more precise metrics of immunocompetence. Four IHGs (I to IV) tracking the equilibrium between CD8+ and CD4+ T-cell counts were computed (**Figure 1A**; **Figure E1C**). Laboratory cutoffs were the lower interquartile bounds of the median CD4+ count in otherwise healthy HIV-seronegative persons (800 cells/mm^3)[26, 27] and an inverted CD4:CD8 T-cell ratio (<1.0) (**Figure 1A**). The CD4+ cutoff was used as ≥800 CD4-cells/mm^3 associated with near-normalized immune status in HIV+ persons[27]. An inverted ratio was used as a cutoff as it is a mathematical reflection of expanded CD8+

levels uncompensated by a concomitant increase in CD4+ T-cell levels. Thus, an inverted ratio marks CD8-CD4 disequilibrium, signifying higher CD8+ levels with relatively higher (IHG-III) or lower (IHG-IV) CD4+ counts (**Figure 1A, B**). To metricize CD4+ levels during SARS-CoV-2 vs. HIV infections, we derived subgrades (suffixes a, b, and c) of IHG-II and IHG-IV using CD4+ cutoffs demarcating AIDS (≤200 cells/mm^3)[52] and the median CD4+ count during primary/early HIV infection (500 cells/mm^3)[26, 27]. While the CD8-CD4 profiles of IHG-IIc and IHG-IVc mark profound CD4+ lymphopenia (≤200 cells/mm^3), IHG-IVc defines the profile of AIDS (**Figure 1B**).

RNA obtained from peripheral blood samples was sequenced and transcriptomic metrics of IR comprised gene expression signatures associated with mortality hazards during COVID-19 (**Figure E1B**; Supplementary methods)[53, 54]. Genes with significantly higher expression levels in study groups signifying nonprogressive COVID-19 were defined as beneficial, whereas genes with higher levels in study groups signifying progressive COVID-19 were defined as detrimental. Significantly enriched gene ontology biologic processes (GO-BP) terms were derived based on the differentially expressed genes. Correspondingly, the GO-BP terms were defined as beneficial and detrimental traits. Gene scores were computed by averaging the z-score normalized expression of all genes comprising the GO-BP term. Gene scores of the traits (GO-BP terms) that associated with 30-day mortality hazards during COVID-19 were examined for their associations with mortality in the FHS. Traits that associated with mortality in the COVID-19 cohort and FHS were examined for their associations with influenza symptom severity.

Statistical analyses

Based on chi-square distribution, we calculated 522 patients provided 92% power to detect a moderate effect size (w=0.17) based on the incidence of death within 30 days of presentation with baseline IHG status at a significance level of 0.05. The statistical tests used for each panel in the figures are detailed in the Supplement. Kaplan-Meier survival curves were derived to illustrate cumulative events. Cox proportional hazards models were used to calculate hazard ratios (HRs) for mortality in the COVID-19 cohort and FHS, and rate ratios (RRs) for recovery rates (hospital length-of-stay) as well as nasal SARS-CoV-2 clearance in the COVID-19 cohort. Multivariable logistic and linear regression models were used to compare secondary outcomes. RNA-sequencing analysis was performed using DESeq[55]. All *P* values are 2-sided and shown without adjustment for multiple testing unless specified. All analyses were performed using R, v3.5.0.

RESULTS

IHG distributions and associations in non-COVID-19 cohorts

Based on median CD8+ and CD4+ counts, the IHGs tracked distinct CD8-CD4 equilibrium/disequilibrium profiles: IHG-I tracked lower CD8-higher CD4, IHG-II tracked lowest CD8-lower CD4, IHG-III tracked highest CD8-higher CD4, and IHG-IV tracked higher CD8-lowest CD4 (**Figure E1D**). In a general population cohort (SardiNIA), across all age ranges, IHG-I was the most common grade and IHG-I was uniformly underrepresented in males (**Figure 1C,D**). The overall prevalence of IHG-I in the SardiNIA cohort was 73%. IHG-I frequency declined progressively with age (85% and 46% in 18-24 and ≥80 years age strata, respectively). Reciprocally, the prevalence of the

other IHGs, especially IHG-II and IHG-IV, increased substantially with age (**Figure 1C**; left). The IHG distribution patterns in younger women with SLE mirrored those of older persons (≥80 years) in the SardiNIA cohort. In therapy-naïve HIV-seropositive adults, higher plasma HIV viral loads induced IHG-IV (**Figure 1C**, right). The hierarchy of the hazard of developing AIDS according to the IHG at presentation was: IHG-IV > IHG-III ~ IHG-II > IHG-I, despite IHG-I and IHG-III marking higher CD4+ counts and IHG-II and IHG-IV marking lower CD4+ counts (**Figure 1E; Figure E1E**). Initiation of antiretroviral therapy associated with reconstitution of IHG-I (**Figure 1C**, far-right).

Thus, the juxtaposition of the IHG distributions from three non-COVID-19 cohorts suggested that IHG-I is the primordial IHG from which the other IHGs emerged in settings of increased antigenic stimulation (e.g., SLE, HIV, aging). Correspondingly, in HIV-seropositive persons, preservation of IHG-I was an indicator of superior IR (i.e., resistance to AIDS progression). Our finding that mitigation of antigenic stimulation associated with reconstitution of IHG-I (**Figure 1C**, far-right) corroborated that degradation of IHG-I related to increased antigenic stimulation rather than chronologic age *per se*. Instead, age may serve as an imperfect proxy for cumulative antigenic experience throughout life. This framework was used to examine whether (i) SARS-CoV-2 infection-associated antigenic stimulation induced similar shifts in IHG distributions across age ranges, and (ii) mitigation of SARS-CoV-2 infection-associated antigenic stimulation associated with reconstitution of IHGs to levels observed in age-matched persons in the SardiNIA cohort.

IHG distribution and associations in COVID-19

The COVID-19 cohort comprised 522 patients, mostly males (*n*=468, 90%) with a median age of 62 (IQR, 47-72) years; 349 (67%) were hospitalized and 173 (33%) were nonhospitalized (**Table 2, Figure E1A, Table E1A**). A total of 224 (43%) patients required respiratory support, including 59 (11%) needing mechanical ventilation (**Figure E1A**, **Table E1B**). Forty-eight (9%) and 69 (13%) patients died within 30 and 120 days of presentation, respectively. The median (IQR) time to death within 30 and 120 days of presentation was 13 (6-17) and 17 (11-36) days, respectively (**Table E1B**).

Cohort characteristics by baseline IHG status are described (**Table 2**). Overall, 21%, 64%, 2%, and 13% individuals presented with IHG-I, IHG-II, IHG-III, and IHG-IV, respectively (*n*=111, 335, 9, and 67, respectively; **Figure 1C**, middle). The median times from symptom onset to presentation (baseline) was 6 (IQR, 2-9) days and did not differ significantly by baseline IHG (*P*=0.26). Individuals presenting with IHG-I tended to be younger with fewer comorbidities. Individuals presenting with IHG-IV vs. IHG-I were older [median age (IQR), 69 (61-78) vs. 51 (42-65) years, respectively; *P*<0.001] and a greater proportion had comorbidities, including chronic kidney disease and dementia (**Table 2, Table E1D**). No persons were receiving COVID-19-directed therapies at baseline; significantly more patients presenting with IHG-II and IHG-IV vs. IHG-I subsequently received COVID-19-directed therapies (e.g., remdesivir, corticosteroids; 41% vs. 9%, *P*<0.001**; Table E1E**).

Akin to the SardiNIA cohort, IHG-I was overrepresented in females vs. males in the COVID-19 cohort (35% vs. 20%; *P*=0.01; **Figure 1C**). Conversely, a lower proportion of females vs. males presented with IHG-II (48% vs. 66%; *P*=0.01; **Figure 1C**). As in the SardiNIA cohort (**Figure 1C**, left), IHG-I frequency declined and IHG-II and IHG-IV frequencies increased with age in the COVID-19 cohort (**Figure 1F**, upper-left stacked bars). However, at both the overall cohort level as well as within comparable age ranges, IHG-I was underrepresented, whereas IHG-II and IHG-IV were overrepresented in the COVID-19 vs. SardiNIA cohort (**Figure 1C**; **Figure 1E**; **Figure 1F**, upper-left stacked bars). Overall cohort-level differences in proportions were 21% vs. 73% for IHG-I, 64% vs. 22% for IHG-II, and 13% vs. 3% for IHG-IV (*P*<0.001 for COVID-19 vs. SardiNIA inter-cohort differences). Additionally, while hospitalization rates increased with age, within each age stratum, hospitalized patients were more likely to have IHG-II and IHG-IV at presentation (**Figure 2A**). Conversely, nonhospitalized patients were more likely to have IHG-I (**Figure 2A**). IHG distributions were similar in younger and older patients who required respiratory support and/or died (**Figure 1C**; **Figure E1F**).

The underrepresentation of IHG-I vs. overrepresentation of IHG-II and IHG-IV was attributable to SARS-CoV-2 infection as, during convalescence, younger and older COVID-19 survivors reconstituted IHG frequencies to levels found in their corresponding age groups in non-COVID-19 cohorts (SardiNIA cohort and healthcare workers; **Figure 2B** vs. **1C**; **Figure E2A**). The IHG reconstitution patterns assigned patients to the IR-dependent COVID-19 phenotypes (**Table 1**). Phenotype 1 corresponded to preservation of superior IR (IHG-I) before and during early COVID-19. Phenotype 2 corresponded to

presentation with a deficit in IR (IHG-II or IHG-IV) but reconstitution of IHG-I (reflecting a diathesis to degrade IHG-I during COVID-19). Phenotype 3 corresponded to presentation with and maintenance of IHG-II or IHG-IV during convalescence, suggesting that these grades may have antedated COVID-19.

The 30-day mortality was lowest among patients with IHG-I compared to IHG-IV and IHG-II (1%, 16%, and 11%, respectively, *P*<0.001; **Table E1B**; **Figure E2B**). Each one increase in age independently associated with mortality (IHG-adjusted HR, 1.05; 95% CI, 1.03-1.08), as well as likelihood of hospitalization (IHG-adjusted OR, 1.06; 95% CI, 1.01-1.07), and need for respiratory support (IHG-adjusted OR, 1.04; 95% CI, 1.02-1.05). An independent association of sex with these outcomes was not observed (data not shown). After adjusting for age and sex, presentation with IHG-I vs. other grades was associated with a lower HR for 30-day mortality (aHR, 0.12; 95% CI, 0.02-0.87) and 120-day mortality (aHR, 0.17, 95% CI, 0.04-0.69) as well as a lower odds ratio (OR) for hospitalization (aOR, 0.16; 95% CI, 0.10-0.26) and mechanical ventilation (aOR, 0.06; 95% CI, 0.01-0.45), and a more rapid recovery rate (aRR, 2.08; 95% CI, 1.40-3.07) (**Figure E2B**).

Compared with presentation with IHG-I, the age-adjusted HR for 30-day mortality in patients presenting with IHG-II or IHG-IV was 8.05 (95% CI, 1.10-59.09) and 9.08 (95% CI, 1.16-71.36), respectively. Despite similar mortality HRs, IHG-II and IHG-IV were tracking individuals with distinct features and outcomes. A greater proportion of individuals presenting with IHG-IV vs. IHG-II were older (≥60 years; 78% vs. 57%; *P*=0.002), progressed according to the clinical ordinal scale (61% vs. 41%; *P*=0.003,

Table E1B), and required mechanical ventilation (24% vs. 13%, *P*=0.02). For these reasons, and because IHG-IV is the hallmark CD8-CD4 profile of therapy-naïve HIV-seropositive persons (**Figure 1B**,**C**), we examined the differences in the origins and associations of IHG-II and IHG-IV subgrades (**Figure 1B**).

Most [98% (513 of 522)] patients in the COVID-19 cohort were HIV-seronegative; of these, 13% (*n*=67) presented with IHG-IIc or IHG-IVc. A greater proportion of hospitalized vs. nonhospitalized HIV-seronegative patients presented with IHG-IIc (15% vs. 1%, respectively; *P*<0.001) or IHG-IVc (4% vs. 0%, respectively; *P*=0.004; **Figure 2C**). During convalescence, no patient had IHG-IIc or IHG-IVc and few patients manifested IHG-IIb (6%) and IHG-IVb (4%) (**Figure 2D**; **Figure E2C**). This finding suggests that these subgrades were induced during COVID-19. Additionally, there was high correspondence between the IR level (IHG status) reconstituted during convalescence and IR level during acute COVID-19 (**Figure 2D**). Nearly all (92%) patients who presented with IHG-I preserved IHG-I during convalescence. The proportion reconstituting IHG-I was progressively lower in individuals presenting with IHG-IIa, IHG-IIb, and IHG-IIc (57%, 44%, and 20%, respectively). Meanwhile, 46% of the patients who presented with IHG-IV persisted with IHG-IV during convalescence (**Figure 2D**). These paired baseline-convalescence IHG distribution patterns indirectly indicate the possibility that pre-COVID-19 IHG status impacts IHG status at presentation during acute COVID-19.

The age-adjusted OR for hospitalization associated with IHG-II subgrades and IHG-IVb/c vs. IHG-I at baseline were comparable to or greater than the IHG-adjusted OR of

hospitalization associated with older age (**Figure 1F**; **Figure E2D**). Although the probability of presenting with IHG-I declined with age (**Figure E2E**), the modeled probability of hospitalization for a 30-year-old patient presenting with IHG-IIc (80%; 95% CI, 48%-95%) was similar to that modeled for a 95-year-old patient with IHG-I (81%; 95% CI, 67%-90%; **Figure 2E**). Presentation with IHG-IV showed a similar increased probability of hospitalization but lower than that associated with IHG-IIc (**Figure 2E**). The age-independent prognostication of hospitalization by baseline IHG status was attributable to our finding that, unlike aggregated lymphocyte values by age, lymphocyte values by IHG status are range-bound across age (**Figure 1F**). Hence, IHGs provide a uniform metric of IR across age.

The age-adjusted hazard of 30-day mortality was increased by a factor of 19.00 (95% CI, 2.47-146.28) with baseline IHG-IIc and 12.15 (95% CI, 1.33-111.15) with baseline IHG-IVc compared with baseline IHG-I (**Figure 3A**, **Figure E3A**). Correspondingly, 30-day mortality rates were highest among patients presenting with IHG-IIc (0.29; 15 deaths in 52 patients with baseline IHG-IIc; 95% CI, 0.17-0.43) and IHG-IVc (0.25; 4 deaths in 16 patients with baseline IHG-IVc; 95% CI, 0.07-0.52), yielding absolute risk differences in mortality of 0.28 (95% CI, 0.16-0.40) and 0.24 (95% CI, 0.03-0.45), respectively. In patients presenting with IHG-I, the risk difference was 0.01 (1 of 111 deaths; 95% CI, 0.00-0.05).

Compared with baseline IHG-I, recovery rates were slowest with IHG-IVc (aRR, 0.12; 95% CI, 0.04-0.30) followed by IHG-IIc (aRR, 0.33; 95% CI, 0.20-0.55; **Figure 3B**; **Figure**

463 **E3B**). Additionally, the likelihood of (i) hospitalization, (ii) manifesting as an increase in
464 the clinical ordinal scale, (iii) need for any respiratory support, and (iv) dying within 30 or
465 120 days of presentation, was lowest to highest in patients presenting with IHG-IVa
466 followed by IHG-IVb, IHG-IIb, IHG-IVc, and IHG-IIc (**Figure E3C, E4A-C**; **Table E1B,G**).
467 The strength of the associations between baseline IHG status and these outcomes were
468 comparable to or greater than those of older age and were independent of age and body
469 mass index (**Supplementary notes 1** and **2**, **Table E1F, G**).
470
471 Correspondingly, while peak IL-6 levels during the disease course were higher in
472 hospitalized patients and nonsurvivors, IL-6 levels were highest with baseline IHG-IIb/c
473 and IHG-IVb/c (**Figure 3C; Supplementary note 3**). Additionally, daily monitoring of
474 IHGs revealed varied IHG reconstitution patterns, and improvements in IHG status
475 presaged declines in plasma IL-6 levels during recovery (**Figure E5, E6; Supplementary**
476 **note 4**).
477
478 Seropositivity for CMV has been associated with the immunosenescence of age as well
479 as changes in CD4+ and CD8+ lymphocyte levels (e.g., the immune risk phenotype that
480 tracks an inverted ratio and CMV seropositivity)[56-60]. Because of these associations, we
481 examined whether the associations of IHGs with outcomes were attributable to CMV
482 seropositivity. Predictably, CMV seropositivity rates increased with age in the COVID-19
483 cohort; however, CMV serostatus did not independently associate with the outcomes of
484 mortality, hospitalization, or respiratory support (**Supplementary note 5**). In contrast,
485 baseline IHGs associated with these outcomes independent of CMV serostatus

(**Supplementary note 5**). This independent association may relate to our finding that CMV seropositivity was differentially distributed between IHG-II vs. IHG-IV (**Supplementary note 5**). A greater proportion of individuals presenting with IHG-II (61%) were CMV-seronegative, whereas a greater proportion of persons presenting with IHG-IV (74%) were CMV-seropositive, and nearly 50% with IHG-I were CMV-seropositive (**Table 2**).

Baseline IHG, nasal SARS-CoV-2 levels, and local host response

Baseline IHG-I, IHG-II, and IHG-IV associated with relatively rapid, intermediate, and delayed clearance, respectively, of nasal SARS-CoV-2 levels (**Figure 3D**; **Figure E7A**; **Table E4**). Compared with baseline IHG-I, SARS-CoV-2 clearance rates were significantly slower by 87% (RR, 0.13; 95% CI, 0.02-0.82) with IHG-IV and trended to be slower by 72% (RR, 0.28; 95% CI, 0.05-1.44) with IHG-II (**Figure E7B**). Correspondingly, SARS-CoV-2 levels were higher in nonsurvivors and patients requiring mechanical ventilation (**Figure E7C**). Genes in the nasal transcriptome whose expression levels associated with both lower SARS-CoV-2 levels and increased survival related to preservation of epithelial integrity as well as robust antiviral and Th2 responses and controlled inflammatory responses (**Figure E8; Tables E5A-C, E6A; Supplementary note 6**). Genes associated with higher SARS-CoV-2 levels also correlated with higher levels of *ACE2*, the SARS-CoV-2 receptor[61]; these genes related to virus-induced inflammation (**Figure E8B**; **Table E5D**).

Unique and shared traits influencing mortality

Comparisons of study groups signifying nonprogressive and progressive COVID-19 identified 42 detrimental and 9 beneficial traits (GO-BP terms) and 28 beneficial genes (**Figure E8A, Tables E6B, E7**). These traits/genes segregated into four categories, depending on whether higher levels of detrimental traits and lower levels of the beneficial traits/genes associated with increased mortality hazards in either, both, or neither the COVID-19 cohort and FHS (**Figure 4A**; **Figure E9; Table E8A-B**). Category 1 comprised 17 detrimental and 6 beneficial traits, along with 28 beneficial genes whose levels defined a unique IC^{low}-IF^{high} state associated with increased mortality hazards only in the COVID-19 cohort (**Table E8A, B**). The unique IC^{low} state related to lower levels of the beneficial traits/genes linked to MHC class II-dependent antigen processing/presentation, the tyrosine signaling pathway, and HLA genes involved in T-cell costimulation (e.g., GO-BP terms 28, 29, and 33, respectively; **Figure 4A**). The unique IF^{high} state related to higher levels of the detrimental traits linked to the inflammatory response to virus (e.g., GO-BP terms 1, 5, and 15 corresponding to type I interferon (IFN) signaling pathway, response to virus, and IFNγ-mediating signaling pathway, respectively; **Figure 4A**).

Category 2 comprised 12 detrimental and 3 beneficial traits whose levels defined a shared IC^{low}-IF^{high} state associated with mortality hazards in both the COVID-19 cohort and FHS (**Table E8C**). The shared IC^{low} state related to lower levels of shared beneficial traits linked to T-cell costimulation, T-cell signaling, and immune responses with genes (e.g., *CCR5*, *CCR7*, *IL7R*) essential for the integrity of T-cell homeostasis (e.g., GO-BP terms 30, 31, and 32). The shared IF^{high} state related to higher levels of shared detrimental traits related to inflammatory responses commonly elicited during antigenic challenges

532 experienced during aging (e.g., GO-BP terms 4 and 13 corresponding to defense
533 response to gram-positive bacteria and response to lipopolysaccharide, respectively;
534 **Figure 4A**; **Figure E10**; **Table E8C**). Category 3 comprised 8 detrimental traits
535 associated with an increased mortality hazard that achieved statistical significance only
536 in the FHS (e.g., GO-BP terms 24, 25; **Figure 4A**; **Figure E8A)**. Category 4 comprised 5
537 detrimental traits that did not achieve statistical significance for mortality hazards in either
538 the COVID-19 cohort or FHS (**Figure E9**).
539
540 The unique and shared IC^{low}-IF^{high} states associated with nonsurvivors, patients requiring
541 mechanical ventilation, older individuals, and those presenting with IHG-II or IHG-IV
542 (**Figure 4B**, **Figure E11, Table E9A**). Similar associations were observed with trait levels
543 measured during the disease course (**Figure E12**; **Table E9B, C**). Additionally, baseline
544 levels of 48 of the 51 traits and the 28 beneficial genes associated with baseline IHG
545 status after controlling for age (**Table E9D**).
546
547 Our discovery of a shared IC^{high}-IF^{low} state that associated with a survival advantage in
548 both the COVID-19 cohort and FHS was congruent with four additional salutary
549 associations in non-COVID-19 cohorts. First, akin to our findings in the COVID-19 cohort
550 (**Figure 4B**, **Figure E11**), in non-COVID-19 cohorts (**Figure E13**), the shared IC^{high}-IF^{low}
551 state that associated with COVID-19 survival marked individuals with IHG-I, whereas the
552 shared IC^{low}-IF^{high} state that associated with COVID-19 mortality marked persons with
553 IHG-IIc and IHG-IVc. Second, the shared IC^{high}-IF^{low} state was overrepresented in
554 females vs. males across age in the FHS (**Figure E14A**). In both sexes, levels of the

555 shared IC^{high}-IF^{low} state declined proportionately during aging; however, comparable
556 levels of this state associated with a greater survival benefit in females (**Figure E14B;**
557 **Table E8D**). Third, beneficial traits that defined the shared IC^{high} state co-clustered at high
558 correlation levels with a gene signature [immune age (IMM-AGE)] associated with lower
559 hazards of cardiovascular disease and mortality in the FHS[40] (**Figure E15**).
560 Correspondingly, higher expression levels of the IMM-AGE signature associated with a
561 lower mortality hazard in the COVID-19 cohort (HR, 0.91; 95% CI, 0.84-0.98). Notably,
562 higher levels of the IMM-AGE score associated with a lower abundance of immune
563 markers signifying immunosenescence in the FHS[40]. Fourth, the shared IC^{high}-IF^{low} state
564 was associated with less-severe influenza infection, including after nasal inoculation of
565 influenza virus in otherwise healthy younger adults (**Figure E16**).
566

567 **Discussion**

568 Through evaluations of COVID-19 and non-COVID-19 cohorts, we uncovered the
569 conserved features of a suspected but previously uncharacterized sexually dimorphic,
570 antigen-activated, immunologic program that associates independently with lower
571 immunocompetence and increased inflammation at any age. We propose that relative
572 resistance to activation of this immunologic program is more common in females and
573 signifies IR. Laboratory (CD8-CD4 equilibrium/disequilibrium-based) and transcriptomic
574 (gene expression signatures) metrics signifying preservation of IR were associated with
575 salutary outcomes: a survival advantage in persons either with or without COVID-19, as
576 well as resistance to development of a progressive disease course during infections with
577 SARS-CoV-2, influenza viruses, or HIV. We report on three observations relevant to

understanding the basis for the age-independent and sex-biased differences in susceptibility to developing severe COVID-19, as well as improving clinical care and identifying therapeutic targets for mitigation of progressive COVID-19.

First, we derived readily measurable metrics of IR that predicted all-cause, 30-day COVID-19 mortality independent of age, sex, body mass index, and CMV serostatus. Correspondingly, use of these metrics predicted secondary outcomes that included clinical indicators (e.g., hospitalization, mechanical ventilation) and biomarkers (e.g., plasma IL-6 and nasopharyngeal SARS-CoV-2 levels) indicative of progressive COVID-19. Second, we distinguished and quantified the individual contributions to COVID-19 outcomes of age vs. age-independent deficits in IR that antedated SARS-CoV-2 infection vs. age-independent deficits in IR that are uniquely induced in response to infection. These findings provide support for three novel, IR-dependent COVID-19 phenotypes linked to differential survival risks (**Table 1**), predicated on whether persons had the proclivity to preserve IR before and during COVID-19, at any age. Across age strata, persons preserving metrics indicative of superior IR before and during early COVID-19 were more likely to manifest a survival advantage and nonprogressive COVID-19 (phenotype 1; **Table 1**). Females were more likely to manifest phenotype 1. The distinction between the negative effects of age vs. pre-infection or infection-induced deficits in IR at any age has clinical implications for the prediction and prevention of progressive COVID-19, as well as for the personalization of care (**Supplementary note 7**; **Figure E17**, **E18**). Third, we identified two sets of IR-associated traits linked to immunocompetence or inflammation that associated with survival: one set comprised

601 traits that uniquely associated with survival during COVID-19, whereas the other set
602 comprised shared traits that associated with mortality in persons with or without COVID-
603 19. Both sets of traits may proffer therapeutic targets for mitigation of COVID-19 mortality,
604 whereas the latter set of traits points to therapeutic targets for extending longevity.
605
606 IHG-I signifies high-grade CD8-CD4 equilibrium and represents the primordial IHG from
607 which other IHGs emerge during antigenic challenges (**Supplementary note 7**). The
608 relative prevalence of the various IHGs in a study group is unique to the type and level of
609 antigenic experience or exposures. Consequently, IHG distribution patterns across
610 cohorts differed: SardiNIA (IHG-I > II > IV > III), SLE (IHG-II > IV > I > III), COVID-19
611 (IHG-II > I > IV > III), and HIV (IHG-IV > II > I~III). Hence, HIV-associated and SARS-
612 CoV-2-associated antigenic stimulation preferentially induce CD8-CD4 profiles
613 corresponding to IHG-II and IHG-IV, respectively. Underscoring that IHG-I marks superior
614 IR, in the HIV cohort, presentation with IHG-I, IHG-II, and IHG-IV associated with the
615 lowest, intermediate, and highest AIDS susceptibility, respectively. Paralleling these HIV-
616 related associations, presentation with IHG-I vs. IHG-II or IHG-IV associated in an age-
617 independent manner with a survival advantage vs. disadvantage, as well as other
618 features of nonprogressive vs. progressive COVID-19.
619
620 The inter-cohort differences in IHG distributions underscore that age is an imperfect proxy
621 for antigenic experience. In response to antigenic experience, the prevalence of IHG-I
622 declines with age, increasing the pool of at-risk persons with IHG-II and IHG-IV. Thus, at
623 any age, the presence of IHG-II or IHG-IV vs. IHG-I before COVID-19 likely heightens the

risk of developing progressive COVID-19. This is a parsimonious basis for our finding that, while hospitalization rates increased with age, irrespective of age, patients who were hospitalized, required respiratory support, and/or died were more likely to present with IHG-II or IHG-IV vs. IHG-I. Moreover, presentation with IHG-II or IHG-IV vs. IHG-I associated with delayed nasal SARS-CoV-2 clearance, a feature associated with mortality in our cohort. In a general HIV-seronegative community population, nearly 12% vs. 27% of younger vs. older adults (age <30 vs. ≥60 years) had IHG-II, and about 1 in 25 older adults had IHG-IV. Thus, we suggest that irrespective of age, persons with a diathesis to develop IHG-II or IHG-IV, before or during COVID-19, likely contribute the most to the overall burden of progressive COVID-19.

SARS-CoV-2 infection is unique in that, in the susceptible host, it may transiently perturb pre-existing IR status to levels observed in HIV-seropositive persons. To metricize these perturbations and their contributions to COVID-19 outcomes, we evaluated IHG-II and IHG-IV subgrades, with IHG-IIc and IHG-IVc corresponding to CD8-CD4 profiles linked to profound CD4+ lymphopenia (<200 cells/mm^3) and IHG-IVc reflecting the profile of AIDS. In HIV-seronegative non-COVID-19 contexts, most persons with IHG-II or IHG-IV manifest the IHG-IIa or IHG-IVa subgrades; in the setting of COVID-19, some persons degrade pre-existing IHG-I, IHG-IIa, or IHG-IVa to lower grades/subgrades. However, some persons resisted this degradation, accounting for our finding that, independent of age, baseline IHG status predicted survival and secondary outcomes, generally following a hierarchical pattern (better to worse): IHG-I > IHG-IIa > IHG-IVa > IHG-IVb ≥ IHG-IIb > IHG-IVc ≥ IHG-IIc. The extremes of this spectrum, i.e., IHG-I vs. IHG-IIc or IHG-IVc,

represent persons with high-grade resistance vs. susceptibility to degrade IR (phenotypes 1 vs. 3, respectively). During COVID-19, these extremes associated with lower vs. higher plasma IL-6 levels. Nearly 40% of the individuals who died presented with IHG-IIc or IHG-IVc.

Persons presenting with IHG-IIc and IHG-IVc differed. Compared with persons presenting with IHG-I, presentation with IHG-IIc or IHG-IVc was associated with a ~19- or ~12-fold higher hazard of death in 30 days, respectively, and recovery times that were 67% and 88% longer, respectively. Persons presenting with IHG-IVc vs. IHG-IIc tended to be older, have more comorbidities, were CMV seropositive, and displayed contrasting IHG reconstitution patterns during convalescence. While CMV seropositivity increased with age, CMV serostatus was not associated with mortality. Thus, the IHG at presentation was not stochastic, but likely reflected the antigenic experience of the host before COVID-19 and response to SARS-CoV-2 infection.

Four findings highlight the substantial impact of baseline IHG status on COVID-19 outcomes: (i) compared to presentation with IHG-I, presentation with IHG-IIc increased the absolute risk of 30-day mortality by 28 additional deaths per 100 persons, (ii) compared to presentation with IHG-IIa, presentation with IHG-IIc associated with an excess of 26 additional deaths per 100 persons, (iii) while more older persons presented with IHG-IIc or IHG-IVc, the age-adjusted associations of these grades with COVID-19 outcomes were at least as strong as those associated with older age, and (iv) the

associations of IHG status with COVID-19 mortality were independent of both age and CMV serostatus, as well as body mass index, a risk factor for severe COVID-19[62, 63].

Transcriptomic data support that a switch from IHG-I to IHG-II or IHG-IV before or during COVID-19 may associate with an immunosuppressive, pro-inflammatory state that contributes to mortality. We identified two distinct IC^{low}-IF^{high} states that associated with COVID-19 mortality. The shared IC^{low}-IF^{high} state likely antedated COVID-19, as it associated with mortality not only in persons with COVID-19 but also participants in the FHS, independent of age. Additionally, trait features of the shared IC^{low}-IF^{high} state corresponded to maladaptive host responses to antigenic challenges typically experienced throughout life. The unique IC^{low}-IF^{high} state corresponded to unregulated host responses to SARS-CoV-2 infection and associated with a survival disadvantage exclusively in patients with COVID-19. The unique and shared IC^{low}-IF^{high} states were enriched in persons with IHG-II or IHG-IV. Conversely, the shared IC^{high}-IF^{low} state associated with a survival advantage in both the COVID-19 cohort and FHS, and was enriched in persons with IHG-I, regardless of COVID-19 status. The shared IC^{high}-IF^{low} also associated with less-severe influenza.

Thus, irrespective of COVID-19 status, superior IR was indicated by IHG-I linked to a shared IC^{high}-IF^{low} state, whereas deficits in IR were indicated by IHG-II or IHG-IV linked to shared IC^{low}-IF^{high} states. Females were more successful in preserving indicators of superior IR than males, as well as in manifesting a longevity advantage compared with males in the FHS, even after correction for differences in the levels of IR between the

sexes. Congruently, during COVID-19, more females presented with IHG-I, potentially explaining why the risk of developing progressive COVID-19 is lower in females.

As the baseline IHGs independently predict COVID-19-associated mortality and recovery, balancing IHG status across trial intervention vs. placebo arms may reduce confounding in clinical studies (**Supplementary note 7**; **Figure E18**). Moreover, assessment of IHGs may allow for individualized care and tailoring therapies. During COVID-19, levels of the unique and shared IC^{low}-IF^{high} states were highest in persons presenting with IHG-IIc or IHG-IVc and corresponded to an immunodeficient-hyperinflammatory state characterized by uncontrolled inflammation, inadequate MHC class II responses, deficits in T-cell co-stimulation/signaling, higher plasma IL-6 levels, and higher nasal SARS-CoV-2 levels (**Supplementary note 7; Figure E18**). Gene expression analysis suggests that the failure to mount effective antiviral and immune responses in the nasal compartment may underlie both higher SARS-CoV-2 burden and increased mortality, as well as correlate with higher expression of *ACE2*, the receptor for SARS-CoV-2 [61] (**Supplementary note 6**). Thus, presentation with or rapid advancement to IHG-IIc or IHG-IVc serves as an early indicator of progressive disease, even before worsening respiratory function. Early targeting of the IC^{low}-IF^{high} state in persons presenting with or advancing to IHG-IIc and IHG-IVc may mitigate disease progression. This can potentially be achieved via combinatorial therapies with immunomodulators (e.g., Baricitinib) and anti-inflammatory agents (e.g., interleukin-6 signaling inhibitors).

The IHGs were more precise measures of the conventional metrics of immune status vs. conventional metrics (CD4+ count or CD4:CD8 ratio used alone; **Supplementary note 8**). This observation in conjunction with the strength of the associations of IHGs with COVID-19 outcomes suggest that IHGs hold promise as a pragmatic clinical tool to assess, monitor, and predict clinical outcomes and inflammatory status during COVID-19. Daily monitoring of IHGs (e.g., **Figure E6**) was implemented at our institution to support algorithms in conjunction with clinical assessment for admission, anticipating level of care and duration, and directing therapies. Based on our findings, examples of clinical utility of the IHGs include: (i) initial staging of COVID-19 severity, (ii) monitoring progress of COVID-19 severity, (iii) improved differential diagnosis of worsening oxygenation status attributable to COVID-19 vs. other sources (e.g., patients with improving IHG status would suggest COVID-19 was less likely the cause, suggesting alternative possibilities such as pulmonary embolism or hospital-acquired pneumonia), (iv) identification of patients with poor recovery or persistent COVID-19 (e.g., persistently poor oxygenation, unresolved radiographic findings consistent with COVID-19, positive polymerase chain reaction test for SARS-CoV-2 with low cycle threshold values, and failure to improve IR metrics). We found that all patients in our cohort with presumed persistent COVID-19 had persistent IHG-IIc or IHG-IVc, suggesting that a failure to clear SARS-CoV-2 burden, possibly due to deficits in IR, may contribute to this persistence. In such patients, IHGs were used to help identify those more likely to have persistent COVID-19, warranting aggressive/alternative therapeutic approaches including prolongation or reinitiation of remdesivir, corticosteroids, and/or initiation of immunomodulators (e.g., Baricitinib).

At the time of this paper, the US Food and Drug Administration is strategizing COVID-19 vaccine booster doses for those who are “immunocompromised” and face a greater risk from infection or re-infection[64]. Yet, identifying persons who are “immunocompromised” beyond qualifying comorbidities (e.g., history of cancer, transplant recipients, receiving immunosuppressant medications), or those with advanced age, remains obscure and limited. IHGs track immunocompetence and inflammation status independent of age. For example, up to 14% of a general population manifested IHG-IV, a grade that is highly prevalent in therapy-naïve HIV+ persons. Hence, assessment of IHG status may provide a means to accurately and precisely gauge “immunocompromised” status relevant for prioritization of booster doses and other preventative therapies, regardless of age.

There are limitations of our study. The COVID-19 cohort comprised mostly male veterans, many of whom were older and had comorbidities; these features may not be generalizable. Second, therapies for COVID-19 could confound associations. Treatment decisions in our cohort were not dictated by participation in any concomitant clinical trials, and baseline IHG status was used for defining associations. Third, we were unable to obtain viral cultures. Fourth, defining the association of IHG status with post-acute sequelae of SARS-CoV-2 infection was beyond the scope of this study.

In summary, we identified age-independent, female-biased processes linked to higher immunocompetence and lower inflammation signifying IR that bridge longevity, COVID-

19 survival, and resistance to AIDS and severe influenza. Thus, the IR metrics have value for precision immune health monitoring across lifespan, irrespective of COVID-19 status. Our data favor a mechanistic model wherein gain of detrimental function (inflammation) and loss of beneficial functions (lower immunocompetence) signifying IR deficits independently and synergistically contribute to mortality in persons with or without COVID-19 (**Supplementary note 7**). Across all age ranges, the relative burden of progressive COVID-19 is dependent on the prevalence of individuals with a proclivity to preserve vs. degrade IR before and during COVID-19, with males having a diathesis to degrade IR. The magnitude of the absolute risk differences for 30-day mortality associated with IHG status at presentation underscores the need for a combinatorial approach with immunomodulators and anti-inflammatory agents to mitigate progression of pre-existing IR deficits and/or promote the rapid restoration of the IR status that antedated SARS-CoV-2 infection.

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FIGURE LEGENDS

Figure 1. Immune health grades (IHGs) associations in study cohorts. (**A**, **B**) IHG features. (**C**) Left: IHG prevalence in SardiNIA cohort by sex and age strata and females with systemic lupus erythematosus (SLE). Middle: IHG at presentation in the COVID-19 cohort by sex, hospitalization and survivor status, and nonsurvivors by age. Right: IHG in therapy-naïve HIV+ participants (with known dates of seroconversion) at entry into the Natural History Study by entry viral load (VL; <1K, 1-10K, 10-100K, ≥100K copies/mL; K, $x10^3$). Rightmost: IHGs before and after at least 5 years of antiretroviral therapy (ART). (**D**) IHG prevalence (top) and odds ratio (OR) with 95% confidence intervals (CI) for prevalence of IHG-I (bottom) by sex within age strata. (**E**) Hazard ratios (HRs) with 95% CI of developing AIDS (1987 criteria[65]) in HIV+ participants by entry IHG. H, high; L, low. (**F**) Top-left: IHG prevalence by age strata. $P_{IHG\text{-}I}$ and $P_{IHG\text{-}IV}$ is for the proportion of IHG-I vs. rest and IHG-IV vs. rest across age strata. Top-right: Age strata distribution by IHG subgrades. Middle- left and right: OR with 95% CI for hospitalization. OR by age strata (left) adjusted by baseline IHG status and OR by baseline IHG status (right) adjusted by age strata. Bottom: Median values of CD4+ and CD8+ counts and CD4:CD8 ratio by (left) both hospitalization status and age strata and (right) IHG subgrades. †, P=0.06, *, P<0.05; **, P<0.01; ***, P<0.001.

Figure 2. Association of immune health grades (IHGs) at presentation (baseline) with hospitalization status and reconstitution of IHG during convalescence in a COVID-19 cohort. (**A**) Top: IHG frequencies at baseline by hospitalized (H) and nonhospitalized (NH) status and age strata. Bottom: Odds ratio (OR with 95% CI) for

having IHG-I or IHG-II at baseline by hospitalization status. Percent hospitalized shown by age strata. (**B**) Paired IHG distributions at baseline and during convalescence among 206 COVID-19 survivors overall and stratified by age. (**C**) Distribution of IHG subgrades (as in Figure 1B) in HIV-seronegative persons in the COVID-19 cohort categorized as hospitalized (H) and nonhospitalized (NH). (**D**) Distribution of IHGs reconstituted during convalescence by baseline IHG status. (**E**) The probability (with 95% confidence bands) of hospitalization according to age and baseline IHG. Overall IHG-IV was used in this model as all patients with IHG-IVc were hospitalized and numbers of patients in the other IHG-IV subgrades were small. †, $P = 0.07$, *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Figure 3. COVID-19 outcomes by baseline IHG status. (**A**) Top three plots: Kaplan-Meier curves for 30-day all-cause mortality from days since presentation by baseline IHG status (top); IHG-I and IHG-II subgrades (middle); and IHG-I and IHG-IV subgrades (bottom). Middle: number at risk (No.) indicates patients who had not died or been censored before that time point. Bottom: age-adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) (reference: IHG-I). (**B**) Top three plots: Cumulative hospital discharge estimates within 30 days of presentation among hospitalized patients by baseline IHG status (top); IHG-I and IHG-II subgrades (middle); and IHG-I and IHG-IV subgrades (bottom). Middle: number at risk (No.) indicates patients who had not been discharged or been censored before that time point. Bottom: age-adjusted rate ratios (aRR) with 95% CIs (reference: IHG-I). (**C**) Peak plasma IL-6 levels by hospitalization status, survivorship status in hospitalized patients, and baseline IHG status. (**D**) Levels of SARS-CoV-2 viral transcript burden proxied by $\log_{10}$-normalized counts of SARS-CoV-2

nucleoprotein '*N*' gene sequence in nasal transcriptomes of hospitalized patients by baseline IHG status, depicted as mean ± SE (bands).

Figure 4. Beneficial and detrimental traits in the COVID-19 cohort and Framingham Heart Study (FHS). (**A**) Center: Hazard ratios (95% confidence intervals) of mortality in the COVID-19 cohort (30-day) and FHS (survival over 9 years adjusted by age as a continuous variable). Hazard ratios are depicted for 34 out of the 52 traits identified in baseline peripheral blood transcriptome from 48 patients that were significantly associated with progressive COVID-19. Gene ontology biologic processes (GO-BP) terms (left) were classified as detrimental (#1-26) or beneficial (#27-34) traits and representative genes (right) in each trait are shown. The association of these traits was analyzed in the FHS for 9-year survival. Forest plots are categorized and color-coded to represent shared and unique significant associations (FDR<0.1) in these two cohorts. Figure E9 and Table E8 depict the entire list of traits. (**B**) Gene expression scores for a representative detrimental and beneficial trait in baseline peripheral blood transcriptomes (*n*=48) by hospitalization and survivorship status (NH-S, nonhospitalized survivors; H-S hospitalized survivors; NS, nonsurvivors), age strata, and baseline IHG status.

Table 1. Projected immunologic resilience-dependent COVID-19 phenotypes

Characteristic	Phenotype 1	Phenotype 2	Phenotype 3
Pre-COVID-19 IC-IF state*	IC^{high}-IF^{low}	IC^{high}-IF^{low}	IC^{low}-IF^{high}
SARS-CoV-2-induced IC^{low}-IF^{high}* state	Resistance to induction	Susceptibility to induction	Susceptibility to induction
Corollaries of pre-COVID-19 IC-IF state			
Longevity†	Survival advantage	Survival advantage	Survival disadvantage
Influenza infection severity§	Asymptomatic or mild	Moderate	Severe
AIDS resistance§	High	Moderate	Low
Corollaries of pre-COVID-19 *plus* SARS-CoV-2-induced IC-IF states*¶			
Resistance to progressive COVID-19¶	High	Moderate	Low
Survival¶	Pre-COVID-19 survival advantage preserved	Pre-COVID-19 survival advantage lost	Additive survival disadvantage
Sex bias†¶	Females		Males

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; AIDS: acquired immunodeficiency syndrome

*IC-IF: immunocompetence-inflammation state: IC^{high}-IF^{low} signifies superior immunologic resilience (IR); IC^{low}-IF^{high} signifies a deficit in IR. In COVID-19 patients, phenotype 1 is defined by a pre-COVID-19 IC^{high}-IF^{low} state and resistance to induction of a IC^{low}-IF^{high} state in response to SARS-CoV-2-associated antigenic stimulation; phenotype 2 is defined by a pre-COVID-19 IC^{high}-IF^{low} state and susceptibility to induction of a IC^{low}-IF^{high} state in response to SARS-CoV-2-associated antigenic stimulation, and phenotype 3 is defined by a pre-COVID-19 IC^{low}-IF^{high} state and susceptibility to induction of a IC^{low}-IF^{high} state in response to SARS-CoV-2-associated antigenic stimulation. Corollaries (longevity, influenza infection severity, and AIDS risk) associated with pre-COVID-19 IC-IF states are contrasted with corollaries of pre-COVID-19 plus SARS-CoV-2-induced IC-IF states.

†Longevity evaluated in the non-COVID-19 HIV-seronegative, Offspring cohort of the Framingham Heart Study; survival advantage and disadvantage signify lower and higher hazards of mortality over 9 years, respectively.

‡Evaluated in non-COVID-19 HIV-seronegative, influenza infection challenge and natural influenza infection cohorts.

§Evaluated in a non-COVID-19 HIV infection natural history cohort.

¶Evaluated in a COVID-19 cohort; survival advantage and disadvantage signify lower and higher hazards of mortality, respectively during COVID-19. Additive survival disadvantage refers to the combined effects of pre-COVID-19 IC^{low}-IF^{high} state and the unique infection-induced IC^{low}-IF^{high} state induced in COVID-19 patients.

Table 2. COVID-19 cohort characteristics by Immune Health Grade (IHG) status

Characteristic	Overall	IHG-I	IHG-II	IHG-III	IHG-IV	*P*
n	522	111	335	9	67	
Median age (IQR), yr	62 (47-72)	51 (42-65)	63 (48-72)	62 (41-67)	69 (61-78)	<0.001
Age ≥ 60 yr, no. (%)	284 (54)	35 (32)	192 (57)	5 (56)	52 (78)	<0.001
Male sex, no. (%)	468 (90)	92 (83)	309 (92)	8 (89)	59 (88)	0.04
Race or ethnic group, no. (%)†						0.26
White	152 (29)	43 (39)	90 (27)	4 (44)	15 (22)	
Black	72 (14)	17 (15)	45 (13)	1 (11)	9 (13)	
Hispanic or Latino American	234 (45)	36 (32)	163 (49)	4 (44)	31 (46)	
Asian	2 (0)	0 (0)	2 (1)	0 (0)	0 (0)	
Indian or Alaska Native	4 (1)	1 (1)	3 (1)	0 (0)	0 (0)	
Other	51 (10)	13 (12)	27 (8)	0 (0)	11 (16)	
Unknown	7 (1)	1 (1)	5 (1)	0 (0)	1 (1)	
Median BMI (IQR)‡	30 (27-34)	31 (28-35)	30 (27-34)	29 (28-32)	28 (25-32)	0.02
BMI ≥ 30, no. (%)	281 (56)	70 (66)	178 (54)	4 (50)	29 (45)	0.04
Median time from symptom onset (IQR), days	6 (2-9)	6 (2-17)	6 (3-9)	5 (2-7)	5 (2-8)	0.26
Comorbidities, no. (%)						
Asthma	28 (5)	10 (9)	17 (5)	0 (0)	1 (1)	0.18
Bronchiectasis	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	>0.99
Chronic obstructive pulmonary disease	40 (8)	4 (4)	26 (8)	1 (11)	9 (13)	0.09
Interstitial lung disease	9 (2)	1 (1)	3 (1)	0 (0)	5 (7)	0.01
Liver disease or cirrhosis	38 (7)	5 (5)	25 (7)	0 (0)	8 (12)	0.32
Diabetes	184 (35)	33 (30)	122 (36)	3 (33)	26 (39)	0.59
Chronic kidney disease	110 (21)	13 (12)	70 (21)	1 (11)	26 (39)	<0.001
End-stage renal disease§	8 (2)	0 (0)	4 (1)	0 (0)	4 (6)	0.03
Chronic heart failure	45 (9)	3 (3)	33 (10)	1 (11)	8 (12)	0.04
Hypertension	268 (51)	46 (42)	180 (54)	3 (33)	39 (58)	0.06
Coronary artery disease	64 (12)	8 (7)	45 (13)	1 (11)	10 (15)	0.27
Connective tissue disease	13 (2)	3 (3)	6 (2)	0 (0)	4 (6)	0.26
Myocardial infarction	4 (1)	0 (0)	3 (1)	1 (11)	0 (0)	0.09
Atrial fibrillation	37 (7)	7 (6)	24 (7)	0 (0)	6 (9)	0.91
Peripheral vascular disease	30 (6)	4 (4)	18 (5)	0 (0)	8 (12)	0.15
Cerebrovascular accident	33 (6)	5 (5)	18 (5)	1 (11)	9 (13)	0.06
Active, lymphoma	3 (1)	0 (0)	1 (0)	0 (0)	2 (3)	0.12
Active, leukemia	2 (0)	0 (0)	1 (0)	0 (0)	1 (1)	0.31
Active, solid tumor	11 (2)	1 (1)	5 (1)	0 (0)	5 (7)	0.03
History of cancer	34 (7)	7 (6)	14 (4)	2 (22)	11 (16)	0.001

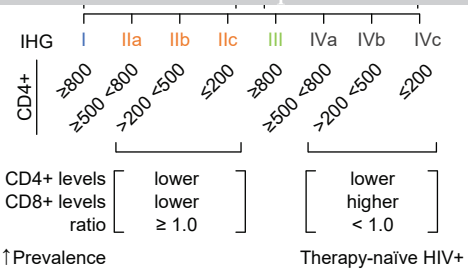
HIV	9 (2)	1 (1)	7 (2)	0 (0)	1 (1)	0.90
Dementia	43 (8)	5 (5)	25 (7)	0 (0)	13 (19)	0.009
Asplenia	2 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0.09
Smoking status						0.006
Current smoker	45 (10)	17 (20)	24 (8)	2 (33)	2 (3)	
Former smoker	82 (19)	12 (14)	55 (19)	0 (0)	15 (24)	
Clinical ordinal scale — no. (%)[¶]						<0.001
1	29 (6)	19 (17)	8 (2)	2 (22)	0 (0)	
2	137 (26)	53 (48)	70 (21)	4 (44)	10 (15)	
3	5 (1)	3 (3)	2 (1)	0 (0)	0 (0)	
4	225 (43)	31 (28)	162 (48)	3 (33)	29 (43)	
5	94 (18)	4 (4)	68 (20)	0 (0)	22 (33)	
6	7 (1)	0 (0)	4 (1)	0 (0)	3 (4)	
7	24 (5)	1 (1)	20 (6)	0 (0)	3 (4)	
8	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	
Cytomegalovirus seropositivity — no. (%)	231 (47)	52 (51)	123 (39)	7 (88)	49 (74)	<0.001
Initial Setting						<0.001
Non-Hospitalized — no. (%)	173 (33)	76 (68)	79 (24)	7 (78)	11 (16)	
Hospitalized — no. (%)	349 (67)	35 (32)	256 (76)	2 (22)	56 (84)	

COVID-19, coronavirus disease 2019; IHG, immune health grade; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range.
[†]Race or ethnicity and sex was as recorded in electronic medical record.
[‡]Body mass index is the weight (kilograms) divided by the square of the height (meters).
[§]End-stage renal disease was defined as requiring hemodialysis.
[¶]Scores on the clinical ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, receiving noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, death.

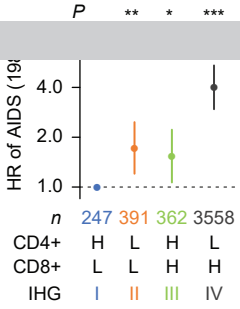
A

IHG	R… ≥		CD8-CD4	
I	+	+	lower	higher
II	+	–	lower	lower
III	–	+	higher	higher
IV	–	–	higher	lower

B



E



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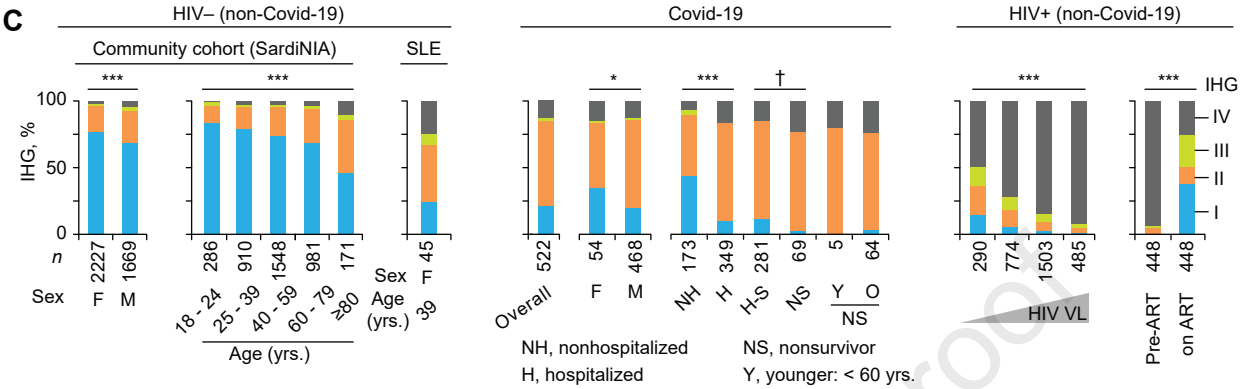

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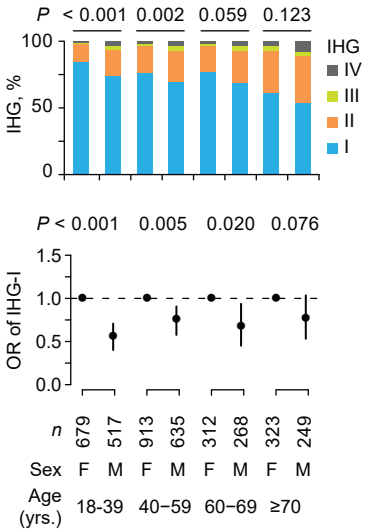

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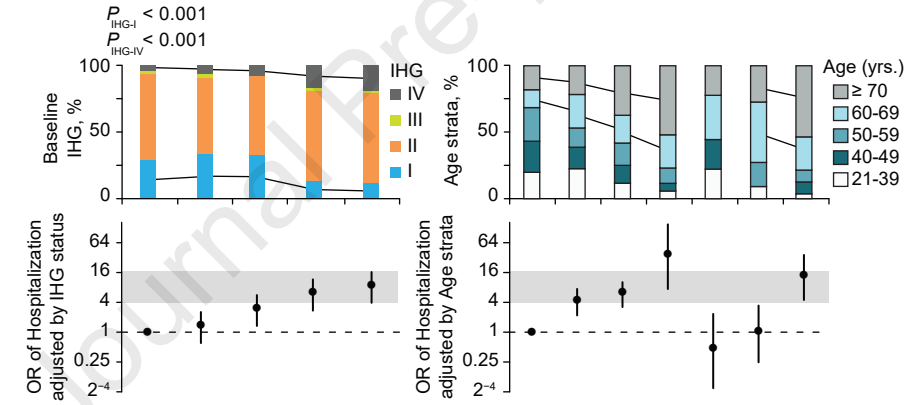
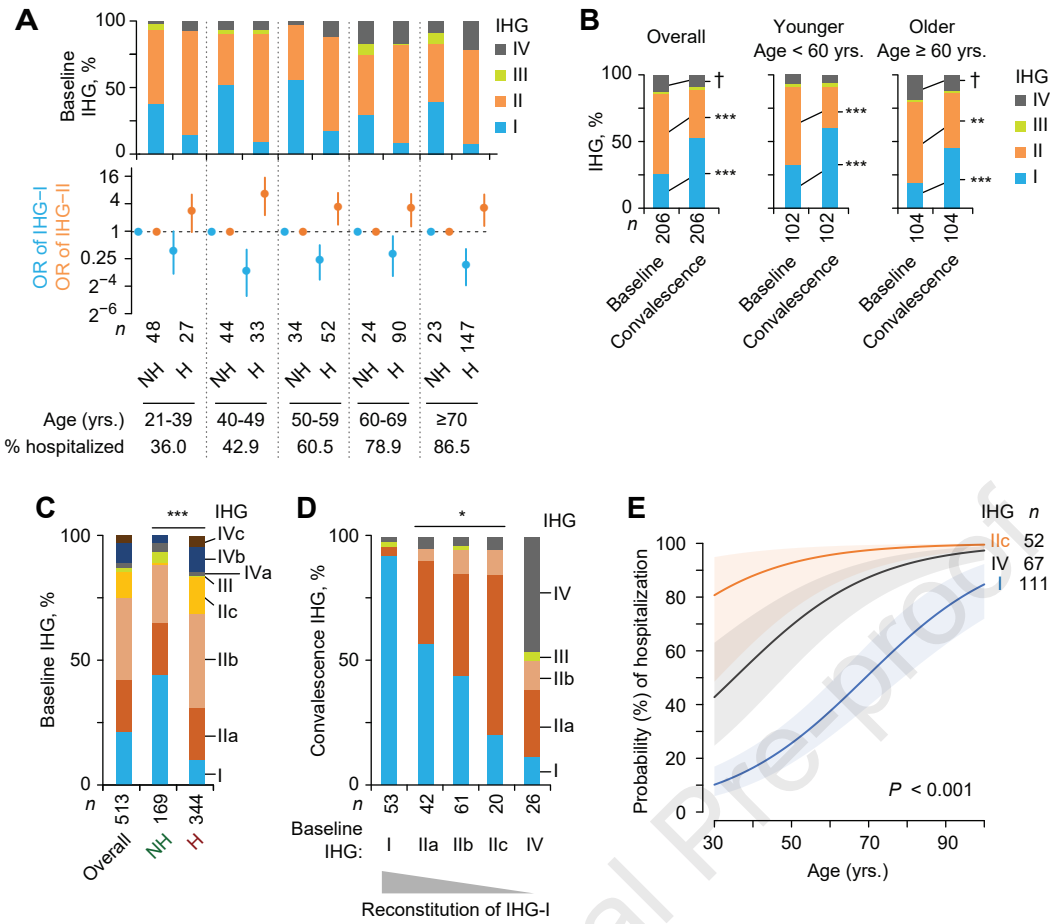
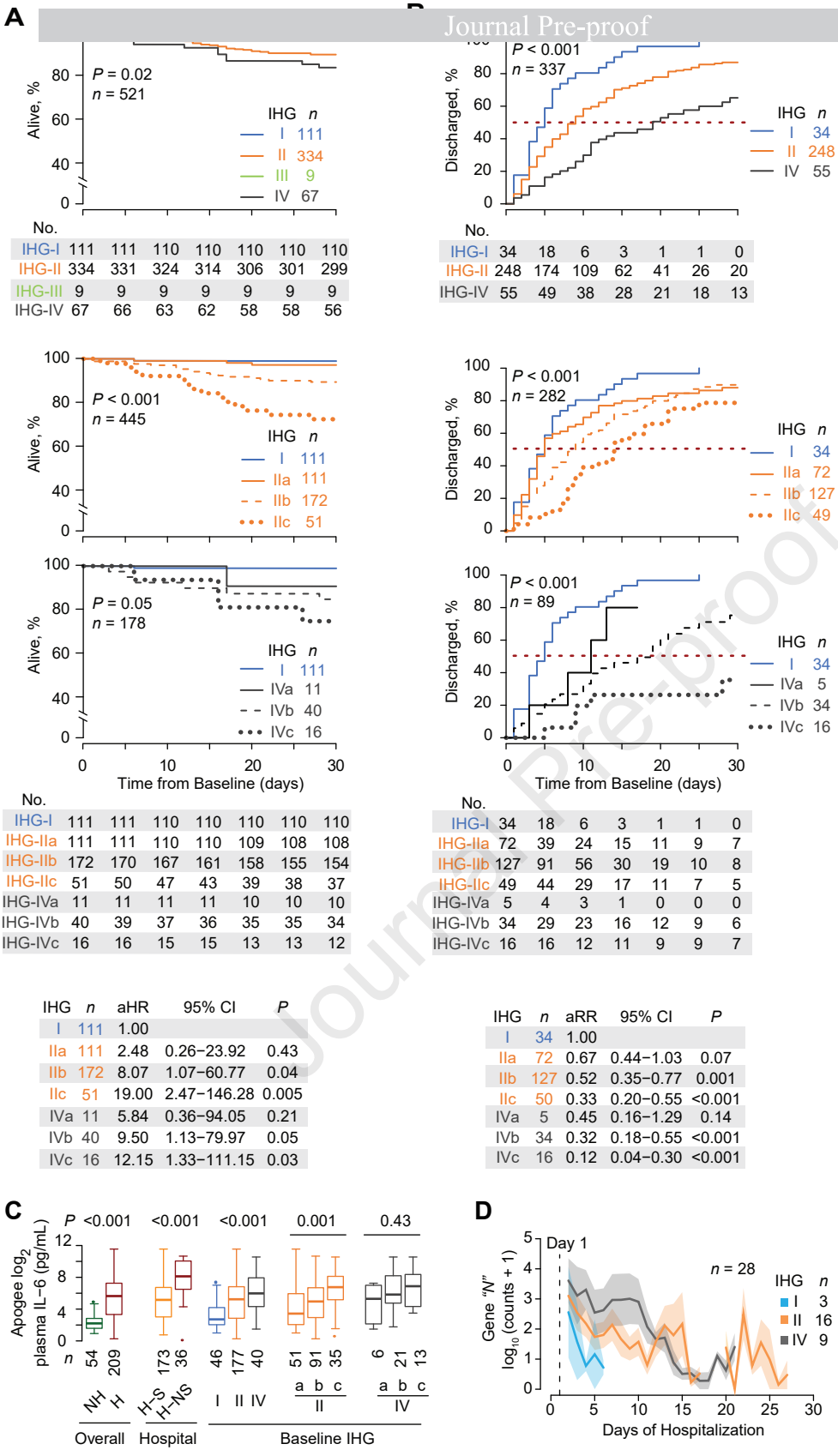


	Age (yrs.)	21–39	40–49	50–59	60–69	≥70
	n	75	77	86	114	170
no	CD8+	398	374	368	448	363
yes	CD8+	319	181	204	201	160
no	CD4+	673	854	820	647	752
yes	CD4+	541	359	394	390	340
no	Ratio	1.75	2.13	1.87	1.70	1.59
yes	Ratio	1.57	2.07	1.94	1.99	1.81

Hospitalized

IHG	I	IIa	IIb	IIc	III	IVa	IVb/c
n	111	111	172	52	9	11	56
	540	322	217	83	1196	704	535
	408	296	151	70	1542	911	374
	1024	638	377	171	844	578	373
	1001	623	328	145	1352	615	269
	2.07	1.99	1.70	2.06	0.77	0.89	0.85
	2.57	2.16	2.12	1.91	0.88	0.78	0.75





A

#	Peripheral blood GO-BP Terms	Covid-19 cohort	Framingham cohort	Representative genes	
1					
2	organ regeneration			*CCL2, CDK1, CDKN1A, FLT3, GAS6*	detrimental traits
3	innate immune response			*APOBEC3A/B, C1QA/B/C, DEFA3/4*	
4	defense response to Gram-positive bacterium			*C5AR1, HIST1H2BC/D,F,G/K, MYD88, TLR2*	
5	response to virus			*APOBEC3A/B, DHX58, HERC5, IFITM1/3, MX1*	
6	immune response			*CCL2/8, CXCL10*	
7	defense response to virus			*AZU1, ISG20, PML, RSAD2,*	
8	cellular response to lipopolysaccharide			*AXL, GAS6, IFIT2/3, IFNAR1, OAS1, STAR*	
9	response to drug			*FOSL1, IGFBP2, IL10, PTEN, STAT3*	
10	leukocyte migration			*FN1, ITGB3, LYN, SELL*	
11	immune response			*CCR1/2, IL18RAP, TLR2/4/6/10*	
12	innate immune response			*CAMP, DDX58/60, FCER1G, IFIT5, TLR3/5/7*	
13	response to lipopolysaccharide			*FAS, FLR2/4, IDO1, IRAK3, JAK2, S100A8*	
14	response to IFNγ			*BST2, MEFV, NUB1, SP100*	
15	IFNγ−mediated signaling pathway			*IFNGR1, JAK2, OAS1/2/3, STAT1, TRIM5/21/22/25/38*	
16	inflammatory response			*C5, CCRL2, CXCR1, IL27, ILIB, ILIORB, TLR1/8/10*	
17	apoptotic process			*CASP1/3/4/5/7/10, C1D/10, IL1B, TNFAIP3, TNFSF8/10/14*	
18	positive regulation of IL-8 production			*DDIT3, NOD2, SERPINE1, TLR2/3/4/5/7*	
19	positive regulation of NF−kappaB transcription factor activity			*EIF2AK2, LTF, NLRC4, S100A9/12, TAB2/3,*	
20	JAK−STAT cascade			*IL31RA, NMI, PIAS1, SOCS1/3, STAT2*	
21	interleukin−1 beta secretion			*ABCA1, AIM2, CD36, GBP5*	
22	response to nutrient			*ACSL3/4, PPARG, SLC6A19/8A1*	
23	movement of cell/subcellular component			*IGF1, TPM1/4, VNN1/2*	
24	regulation of inflammatory response			*ANXA1, BCL6, IL1R1, PSMA6*	
25	MyD88−dependent toll−like receptor signaling pathway			*IRAK3, MYD88, TLR1/2/4/5/6/7/8/10*	
26	activation of MAPKK activity			*MAP3K1/2/5/8/13*	
27	SRP−dependent cotranslational protein targeting to membrane			*RPL5/7/9/11/17/21/23/26/31/34, RPS7/3A/17/24/26/27/27A*	beneficial traits
28	Ag processing/presentation of peptide or polysaccharide Ag via MHC class II			*HLA-DB1/2, HLA-DM/A/B, HLA-DR1/3/4*	
29	transmembrane receptor protein tyrosine kinase signaling pathway			*CD7, CD8A/B, LCK, LTK, SHE2, ZAP70*	
30	T cell costimulation			*CD28, CD4OLG, DPP4, HLA-DRB1/5, ICOS*	
31	T cell receptor signaling pathway			*CD3D, CD3G, CD28, HLA-DRB1/5 PLCG1, RPS27A*	
32	immune response			*CCL4L2, CCR5, CCR7, CXCR5, FCER2, IL7R, IL24, TCF7*	
33	T cell costimulation			*CD4/5, HLA-DPA1/B1, HLA-DQB1/2, HLA-DRB1/3/4/5*	
34	*28 beneficial genes			*ALOX15, CXCR5, ID3, IL5RA*	

Hazard Ratio: 2−4, 0.25, 1, 4, 16, 64, 256 | 0, 0.5, 1, 1.5, 2, 2.5, 3

lower — higher | longer — shorter

mortality | lifespan

*not a GO-BP term

- Significant in Covid-19 only (Category 1)
- Significant in both cohorts (Category 2)
- Significant in Framingham only (Category 3)
- No significant association with mortality hazard

B