Figure 1. Nasopharyngeal swab viral loads and severity of disease compared across infants compared with older children. Abbreviation: Ct, cycle threshold.

Older children and adolescents ranged from 1 year to 21 years of age. Mean NP viral load was significantly higher in infants as compared with older children and adolescents (mean Ct, 21.05 vs 27.25; $P < .01$) (Figure 1). However, a significantly lower proportion of infants had severe disease as compared with the older patients (n = 1 [5%] vs n = 12 [32.4%]; $P = .02$). Mean time to test positivity from symptom onset was lower in infants than older children (2 vs 3.8 days, $P < .01$). Similar proportions in both groups were tested within 7 days of symptom onset (91.2% vs 100%, $P = .47$).

Our report suggests that symptomatic infants have higher NP viral loads at presentation but develop less severe disease as compared with older children and adolescents. Whether this is attributable to slightly earlier presentation to clinical care versus host biology requires investigation. These data have implications for mitigating spread, especially in congregate settings (eg, child care centers) or hospital units (eg, neonatal ICUs) that serve this group.

Note

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Evaluating Immune Dysregulation in Patients With COVID-19 Requires a More Accurate Definition of the CD45RA$^+$ T-cell Phenotype

To the Editor—The coronavirus disease 2019 (COVID-19) pandemic has disproportionally affected the elderly. The recently published study conducted in Wuhan, China, by Qin et al indicated dysregulation of the immune response specifically related to T lymphocytes, suggesting that they are highly involved in the pathophysiology of COVID-19 [1]. T-cell dysregulation is a major contributor to age-related changes of the immune system in the elderly, where T-cell responses become defective. The causes of immunodeficiency are multifactorial, including T-cell phenotypic changes, signal transduction failure, and thymic involution [2, 3]. Dysregulated T-cell responses have been linked to a variety of different diseases typically seen in the elderly, notably cardiovascular disease and Alzheimer's [4, 5]. Furthermore, an immune phenotype known as the immune risk phenotype (IRP) has been used as a marker to track these changes, and is defined by a low CD4:CD8 T-cell ratio and an expansion of $CD8^+CD28^-$ T cells in those cytomegalovirus seropositive [6]. It has been shown that IRP-positive individuals have an expansion of $CD8^+$ effector memory T cells (T_{EM} cells) that are low functioning and late-differentiated, causing memory inflation [7].

The recent COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2, has disproportionately impacted the elderly, with severe cases being linked to increases in proinflammatory cytokines in serum [1]. Qin et al sought to characterize the T-lymphocyte responses in COVID-19, with aims to differentiate between nonsevere and severe cases. The severe cases had a significantly higher average age compared to the nonsevere cases, indicating a worse outcome in the elderly. Additionally, the severe group had an increased incidence of cardiovascular

disease as compared to the nonsevere population. As the IRP is seen at increased levels in the elderly and has been associated with increased incidence of cardiovascular disease, it would be interesting to see the significance of the IRP in terms of COVID-19 response.

The Wuhan study also identified several differences in T-cell populations between the severe and nonsevere COVID-19 cases. Most notably, there were significantly higher levels of $CD3^+CD4^+CD45RA^+$ T cells in the severe cases, which was attributed to increases in naive cells. Although naive T cells are characterized by the presence of a combination of surface markers including CD45RA, this marker alone cannot be used to define naive subsets. Furthermore, CD45RA is re-expressed during late differentiation and is part of a proinflammatory phenotype identified in the elderly [8]. This terminally differentiated T-cell population has been associated with immune dysregulation in the elderly and is further characterized by low CD28 and increased CD57 expression [9].

The Wuhan study failed to further characterize the $CD45RA^+$ T-cell subset, making it impossible to attribute the increase specifically to the naive T-cell subset. Furthermore, the study did not report on $CD8^+CD45RA^+$ T-cell subsets, which are thought to play an important role in the inflammatory aging process. Improved characterization of terminally differentiated $CD45RA^+$ T cells, along with screening for IRP positivity, may be beneficial in identifying those with potential for severe COVID-19.

Notes

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Alterations in Smell or Taste—Classic Coronavirus Disease 2019?

To the Editor—There are increased reports of loss of smell (anosmia) and taste (ageusia) in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19), in particular in the setting of mild disease. The data to date have been presented predominantly from postdiagnosis surveys or retrospective cohort series [1–5]. The pathogenesis is postulated to be due to invasion of the olfactory neuroepithelium and olfactory bulb, which has been seen previously in other coronaviruses, due to the high expression of angiotension-converting enzyme (the receptor that allows virus cellular entry) present in the respiratory system [1, 6]. From a retrospective adult cohort of confirmed SARS-CoV-2 in Germany (n = 72), Luers and colleagues noted that 74% of patients reported anosmia and 69% reported ageusia [7]. Prior to this, from a retrospective cohort study of COVID-19 patients interviewed 5–6 days postdiagnosis, Spinato et al also noted that 64.4% reported alterations in taste or smell [1]. However, both of these studies suffer from the absence of a control group and significant limitation of recall and selection bias. Further, both fail to answer the question of whether anosmia and ageusia are, in fact, more frequent in COVID-19 patients than in those with other upper respiratory tract infections.

To address the identified deficiencies of current data presented, we used a prospectively collected dataset from patients assessed at our institution's COVID-19 screening clinic (Melbourne, Australia) between 1 April 2020 and 22 April 2020 (data collection, see eMethods) to determine if anosmia and/or ageusia were more frequent in patients with confirmed SARS-CoV-2 infection.

A total of 1788 patients underwent clinical evaluation; we identified 40 (2.2%) patients who reported both anosmia and ageusia, with 3.1% (56) for anosmia alone and 4.1% (74) for ageusia alone. Similar proportions were seen in the subgroup of 1236 patients who subsequently underwent SARS-CoV-2 testing (eTable 1). The distribution of symptom prevalence over time is shown in eFigure 1. In those who underwent SARS-CoV-2 testing, anosmia or ageusia was more frequently reported in females and in those who reported more symptoms (eTable1). Of those who reported anosmia or ageusia, 9.3% tested positive for COVID-19 (positive predictive value), while the negative predictive value was 98.5%. Anosmia and/or ageusia were more common in COVID-19–positive than in COVID-19–negative patients