Time to SARS-CoV-2 PCR clearance in immunocompromising conditions: is test-based removal from isolation necessary in severely immunocompromised individuals?

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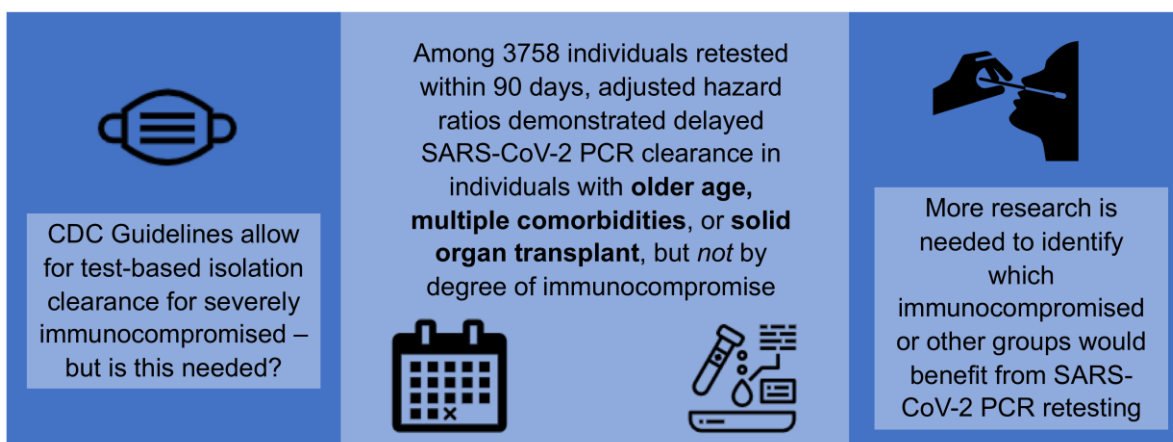
Abstract:

To determine the association between immunosuppression and time to SARS-CoV-2 PCR clearance, we studied 3758 adults re-tested following initial SARS-CoV-2 infection. Cox proportional hazards models demonstrated delayed PCR clearance with older age, multiple comorbidities and solid organ transplant but not by degree of immunocompromise. These findings challenge current retesting practices.

Key Words: SARS-CoV-2, Coronavirus disease 2019 (COVID-19), Virus Shedding, Polymerase Chain Reaction, Immunocompromised Host, Immunosuppression, Disease Severity

Time to SARS-CoV-2 PCR clearance in immunocompromising conditions:

Is test-based removal from isolation necessary in severely immunocompromised individuals?

CDC Guidelines allow for test-based isolation clearance for severely immunocompromised – but is this needed?

Among 3758 individuals retested within 90 days, adjusted hazard ratios demonstrated delayed SARS-CoV-2 PCR clearance in individuals with **older age, multiple comorbidities**, or **solid organ transplant**, but *not* by degree of immunocompromise

More research is needed to identify which immunocompromised or other groups would benefit from SARS-CoV-2 PCR retesting

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Background:

SARS-CoV-2 viral shedding duration and the length of time individuals remain infectious have important implications for transmission and control of Coronavirus Disease 2019 (COVID-19). Immunocompromised individuals shed viruses such as influenza, cytomegalovirus, and norovirus longer than immunocompetent persons [1,2], however little is known about the effect of immunosuppression on duration of SARS-CoV-2 culture or PCR positivity. At least one study demonstrated prolonged SARS-CoV-2 PCR positivity in kidney transplant recipients, albeit without a comparison group [3], and rare cases highlight potential for prolonged, intermittent shedding with immunosuppressive medications [4,5].

Individuals with SARS-CoV-2 infection may remain PCR-positive for many weeks [6–9], but with RNA concentrations and cultivability of infectious virus generally decreasing over time [8,10–13]. Although studies are limited, very few have successfully cultured infectious virus past 20 days of illness [4,5,8,10–13]. One high-risk household contact study found that all transmission events occurred within 5 days of symptom onset in the index patient [14]. Similarly, among 285 individuals with COVID-19 symptom and PCR positivity recurrence following initial symptom resolution, no secondary transmission occurred among 790 household contacts during relapse [15]. Collectively, these data suggest that PCR positivity alone after day 10-20 is not associated with transmission likelihood. United States (US) Centers for Disease Control and Prevention (CDC) guidelines recommend symptom-based clearance from transmission-based precautions in most circumstances, but recommend considering test-based clearance in severely immunocompromised individuals [16]. Test-based clearance, however, can increase hospital cost and length of stay by preventing timely discharge or delaying necessary care [17,18]. The limited studies that compare factors associated with SARS-CoV-2 PCR positivity duration include few immunocompromised patients or lack a comparison group [3,7,9,19]. We therefore sought to compare time to

SARS-CoV-2 PCR clearance by degree of immunocompromise, COVID-19 severity, age, and comorbidities in a large inpatient and outpatient sample.

Methods:

Setting

Boston Medical Center (BMC) is an urban, academic medical center and the largest safety-net hospital in New England. Per CDC and local department of health guidance, in April 2020, BMC implemented a test-based strategy to end isolation precautions for immunocompromised individuals. We used the CDC 'severely immunocompromised' definition for removal of transmission-based precautions: individuals receiving active chemotherapy or chronic high dose steroids (>20mg/day prednisone equivalent for >14 days), who received a transplant in the past year, and those living with HIV with a CD4 count <200 cells/μL or a primary immunodeficiency [16]. Prior to August 2020, we also retested individuals who received acute or chronic biologic therapy and all transplant recipients. Many immunocompetent patients were retested for precaution removal during prolonged inpatient stays, subsequent admissions or emergency department visits, clearance for work or preceding discharge to dialysis centers and congregate living facilities, or for visiting a hospitalized newborn. Before retesting, both inpatients and outpatients required symptom-based clearance per CDC recommendations (initially 14 days after symptom onset and ≥3 days after improvement began; later 10 days after symptom onset or positive test and ≥24 hours after improvement [16]). If the initial retest was positive, guidance recommended retesting every three days until achieving two negative tests ≥24 hours apart.

Retesting occurred inpatient for still-admitted individuals, through a drive-through pre-procedure testing site for asymptomatic patients, at home through an ambulance-based hospital partnership for immunocompromised patients and those unable to present for testing,

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or at an outpatient testing clinic. SARS-CoV-2 PCR tests utilized varied by supply availability. All BMC samples were nucleic acid amplification tests, which received US Food and Drug Administration Emergency Use Authorization (Supplemental Table 1); 93% were nasopharyngeal (NP) specimens performed in-house at BMC, a minority were anterior nares (5.6%) or lower respiratory specimens (1.3%).

Data Collection

We included all adults aged 18-99 years with PCR-confirmed SARS-CoV-2 infection who received ≥1 SARS-CoV-2 PCR retest at BMC within 90 days of initial positive test (as data suggest re-infection is unlikely within the first 90 days [10]). We included all test results recorded in the electronic health record (EHR), including tests performed outside BMC. We extracted data on demographics, medications, anthropomorphic measures, SARS-CoV-2 PCR testing, and underlying medical conditions (classified using International Classification of Diseases, 10th Edition codes from individuals' active condition lists or encounter diagnoses), from BMC's EHR through the COVID Data Repository. Using prospectively designed EHR templates, we captured COVID-19 symptom onset date and medical history. Individuals were assigned one of five mutually exclusive COVID-19 disease severity categories: exclusive outpatient management, non-intensive care unit (ICU) inpatient hospitalization, ICU hospitalization, deceased, or unknown severity (individuals with initial external testing results imported into BMC's EHR). For non-deceased individuals, severity category was based on highest level of care received within 14 days of the initial positive test; all individuals who died prior to the study end date were classified as deceased. We obtained cycle thresholds (Ct) or cycle numbers (CN) for the subset of positive tests with available data (those performed on a platform with recorded quantitative cycle values). The Boston University

Medical Campus Institutional Review Board approved this study as exempt human subject research.

Primary Outcome and Predictor

The primary outcome was time to SARS-CoV-2 PCR clearance, defined as the number of days between first positive and first negative PCR without a subsequent repeat positive PCR. Those without a negative PCR or for whom >1 day elapsed between last positive and first negative PCR were right or interval censored, respectively. For those with date of symptoms onset recorded, we additionally examined time between symptom onset and first negative PCR. Following CDC guidelines, we classified individuals as severely immunocompromised as described above. Moderate immunocompromise included those receiving other immunosuppressive medications, HIV with CD4 ≥200 cells/µL, and transplant >1 year prior (Table 1).

Analysis

We estimated median time to first negative SARS-CoV-2 PCR using Kaplan Meier survival estimators and Cox proportional hazards models accounting for interval censoring. We adjusted multivariable Cox regression models for age, immunocompromise category, and COVID-19 severity as each of these variables has been previously associated with prolonged PCR positivity [3–7], and for all variables with p<0.2 in unadjusted analyses. In a second model we used the same criteria but incorporated only individual immunocompromising conditions or comorbidities with p<0.2 rather than the larger categories. All analyses were done in SAS, version 9.4 (Cary, North Carolina).

We performed four sensitivity analyses. First, to mitigate possible bias in PCR clearance time estimates introduced by infrequent testing, we assessed only individuals with

≥2 negative tests ≤7 days apart, as this group was likely retested more frequently. Second, we assessed only individuals with known symptom onset date with a repeat test occurring within 45 days of the initial positive test. We also separately analyzed individuals hospitalized and those not hospitalized for COVID-19. Finally, for the subset of tests with data available, we plotted Ct by days from initial positive SARS-CoV-2 PCR test, stratified by testing location (inpatient/outpatient). We displayed Abbott tests separately as CNs are not comparable to Cts reported by other platforms [20]. We describe patient characteristics of test values below published thresholds of negligible likelihood of infectious virus (24 for E gene, 32 for N gene) [21,22].

Results:

Among 3758 adults meeting inclusion criteria, mean age was 48.8 (SD 16.4) years, 1677 (44.6%) were male, 1739 (46.3%) identified as Hispanic or Latinx, 1123 (29.9%) as Black, non-Hispanic, and 509 (13.5%) as White, non-Hispanic. In total, 277 (7.4%) were severely immunocompromised, 159 (4.2%) moderately immunocompromised, and 3322 (88.4%) had no documented immunosuppression (Table 1). Approximately half (42.6%) had at least one comorbidity, and 935 (24.9%) had a hospital admission at BMC during their COVID-19 episode. Individuals had a median 3 PCR tests; 1938 received ≥3 tests, 655 received ≥4 tests, and 340 received ≥5 tests. Median time to PCR clearance was 22 (IQR 4-34), 20 (IQR 8-33), and 16 days (IQR 6-29), respectively, for those severely, moderately, and not immunocompromised (Table 1, Supplemental Figure 1).

Adjusted analyses revealed delayed time to SARS-CoV-2 PCR clearance with solid organ transplant (aHR 0.64, 95% CI: 0.42-0.97), diabetes (aHR 0.82, 95% CI: 0.73-0.93), obesity (aHR 0.90, 95% CI: 0.83-0.98), rheumatologic disease (aHR 0.75, 95% CI: 0.57-0.98), ≥3 comorbidities (aHR 0.73, 95% CI: 0.60-0.88), and older age (HR 1.00, 95% CI:

0.99-1.00), but not immunocompromise severity (aHR 1.16, 95% CI: 0.94-1.44 and aHR 0.90, 95% CI: 0.70-1.16 for severely and moderately immunocompromised compared to immunocompetent individuals).

Sensitivity analyses demonstrated similar results though not all associations in the main analysis met statistical significance (Supplemental Tables 2-5). Receipt of an interleukin (IL)-1 or IL-6 inhibitor for COVID-19 treatment was associated with delayed PCR clearance in those with known symptom onset date (aHR 0.68, 95% CI: 0.52-0.89).

For the subset with Ct or CN available (N=754 tests from 601 individuals; 97.5% NP samples), plots stratified by outpatient and inpatient location (Figure 1) demonstrate overall increasing Ct values (decreasing likelihood of infectiousness) over time since infection onset. All tests with Ct <24 after day 20 (the lower threshold cited in the literature above which no tests were culture-positive [22]) occurred inpatient: 8/9 individuals were admitted to the ICU or died and 6/9 were immunocompromised. Only 5 outpatients had Ct <32 after day 20 (all immunocompetent). Abbott CNs were lower overall (Supplemental Figure 2), but only 3 had CN <24 after day 40: one patient with solid organ transplant and HIV, and two non-hospitalized healthy adults under age 30.

Discussion:

We found that solid organ transplant, multiple comorbidities (diabetes, hypertension, obesity, and rheumatologic disease in particular), and older age were associated with delayed SARS-CoV-2 PCR clearance, but observed no significant differences by degree of immunocompromise. Our study presents the largest sample thus far of SARS-CoV-2 PCR retesting in immunocompromised and immunocompetent patients together, allowing comparison by immunocompromised status. Older age and having ≥3 medical comorbidities were most consistently associated with increased time to PCR clearance in sensitivity

analyses, which also revealed delayed clearance in individuals who received an IL-1 or IL-6 inhibitor to treat severe COVID-19. These data align with previous general population median positive PCR duration (16 days from first positive test and 21 days from symptom onset in our study vs. 17-33 days reported in the literature)[6,7,19] and in kidney transplant recipients (50% of solid organ transplant recipients in our study vs. >30% in the literature were PCR positive for >30 days) [3]. We observed prolonged PCR positivity in individuals hospitalized and deceased from COVID-19, but this was not statistically significant; this may have been limited by the 48% without known disease severity (individuals initially tested outside BMC). We did not see associations with sex, general immunosuppression or corticosteroids reported in smaller studies [7,9]. Our data suggest that certain groups of immunocompromised, older, and medically complex individuals appear to have delayed PCR clearance compared with otherwise healthy, young individuals. However, even with a robust sample size, sufficient to show prolonged PCR positivity in solid organ transplant recipients, other immunocompromised groups, including 212 on active chemotherapy, did not have delayed PCR clearance, making a prolonged period of transmission from these individuals similarly less likely.

This study has limitations. First, only one individual received a past-year stem cell transplant, and none received CAR-T cell therapy, so generalizability to the stem cell transplant and other extremely immunosuppressed populations is limited. Second, immunocompromised individuals comprised only 11.6% of the population analyzed, and it is possible we were underpowered to detect significant differences present. However, it is also possible only certain subpopulations of immunocompromised individuals have prolonged PCR positivity, as suggested by differing estimates among subgroups.

Importantly, we did not utilize viral cultures or other means to study transmissibility directly. We therefore cannot conclude anything about infectivity; however, the objective of

our study was to determine whether singling out immunocompromised individuals for SARS-CoV-2 PCR retesting for isolation clearance is useful. Time to SARS-CoV-2 PCR clearance did not differ by immunocompromised status, except in the subpopulation of solid organ transplant recipients, and Ct values increased over time, which generally corresponds with minimal ability to culture infectious virus, particularly after day 20 of illness. Interpreted together, we believe it is unlikely that qualitatively PCR testing all immunocompromised individuals after symptom improvement will provide meaningful information to infer infectivity; however, further studies supported by viral culture are necessary to further inform this and help determine which sub-groups may benefit from quantitative PCR or other (e.g., antibody titer or antigen) testing [12].

As a retrospective EHR record review, systematic retesting at pre-specified intervals did not occur, and the exact day of PCR clearance is unknown. To account for the uncertainty of time between last positive and first negative test, we utilized interval censoring techniques. Sensitivity analyses restricted to only individuals frequently tested also failed to show differences in time to PCR clearance by immunocompromised status. Multiple different assays used, with variable sensitivity and cutoffs, also limit findings, though overall Ct trends across assays were similar.

Finally, use of first positive SARS-CoV-2 PCR test, not symptom onset, likely underestimated total time to PCR clearance. Our sensitivity analysis limited to those with known symptom onset date yielded similar estimates but failed to show any significant differences, albeit with small sample size.

Although initial reports on SARS-CoV-2 and data from other viral infections suggest concern for prolonged SARS-CoV-2 PCR positivity in immunocompromised patients overall, our data do not support this. Furthermore, though sample size prevented multivariable

analysis of the relative risk of low Ct of positive PCR tests performed after illness day 20, severe disease was more common than immunosuppression in individuals with prolonged low Ct values in this cohort, and other studies demonstrate that PCR positivity does not imply infectivity. Lower viral loads seen after day 10-11 of illness are associated with lower likelihood of replication-competent virus [12] and most individuals who have recrudescence of positive SARS-CoV-2 PCR after initial symptom resolution do not appear to still be infectious [13]. Even in rare reported cases of infectious virus cultured weeks after initial infection, some had interim negative retesting, and individuals were symptomatic at later positive culture and PCR testing [4,5]. Without clear evidence of which groups of immunocompromised or other individuals clear PCR later than the general population, or that prolonged asymptomatic PCR positivity corresponds to ongoing transmission risk, the usefulness of qualitative, PCR test-based clearance criteria for severely immunocompromised individuals is unclear. While broad testing strategies are critical to identify new cases, retesting to end isolation may not be warranted, particularly in this resource-constrained global pandemic setting.

Footnotes:

Patient Consent Statement: The Boston University Medical Campus Institutional Review Board approved this study as exempt human subject research. As such, patient consent was not required for this retrospective review of electronic health record data.

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Table 1: Demographic characteristics, comorbidities and time to SARS-CoV-2 PCR clearance in patients followed at Boston Medical Center for SARS-CoV-2 infection and retested within 90 days, March 2020-February 2021

Characteristic	N (%) (N=3758)	Median (IQR) time (days) to first Negative PCR[a]	Unadjusted Hazard Ratio (95% CI)[b]	Adjusted Hazard Ratio (95% CI)[b]	Adjusted Hazard Ratio (95% CI)[b]
Age (Mean, SD, Range)	48.8 (16.4, 18-99)	--	**0.995 (0.992-0.997)**	**0.997 (0.994-1.000)**	**0.996 (0.993-0.999)**
Age Quartiles (years)					
18-35	947 (25.2)	13 (4-28)	Ref.	--	--
36-48	937 (24.9)	16 (5-26)	0.94 (0.83-1.05)	--	--
49-60	933 (24.8)	17 (8-30)	**0.87 (0.78-0.98)**	--	--
>60	941 (25.0)	21 (6-33)	**0.81 (0.72-0.90)**	--	--
Sex					
Male	1677 (44.6)	18 (6-31)	0.97 (0.89-1.05)	--	--
Female	2081 (55.49)	14 (7-29)	Ref.	--	--
Race/Ethnicity					
Black, non-Hispanic	1123 (29.9)	14 (6-27)	**1.10 (1.00-1.21)**	--	--
Hispanic or Latino	1739 (46.3)	18 (6-31)	Ref.	--	--

White, non-Hispanic	509 (13.5)	18 (6-33)	0.95 (0.84-1.08)	--	--
Other Race (non-Hispanic)	128 (3.4)	17 (3-29)	1.06 (0.84-1.34)	--	--
Unknown/Declined	259 (6.9)	15 (7-27)	1.08 (0.91-1.28)	--	--
COVID-19 Severity					
Deceased	91 (2.4)	26 (11-33)	**0.67 (0.50-0.91)**	0.77 (0.56-1.04)	0.76 (0.56-1.03)
ICU	180 (4.8)	21 (2-25)	0.93 (0.77-1.12)	1.01 (0.83-1.22)	1.04 (0.86-1.27)
Hospitalized, no ICU	664 (17.7)	21 (7-32)	**0.84 (0.74-0.96)**	0.91 (0.80-1.04)	0.92 (0.80-1.05)
Not Hospitalized	1012 (26.9)	13 (7-27)	Ref.	Ref.	Ref.
Unknown	1811 (48.2)	16 (7-29)	**0.88 (0.79-0.97)**	**0.86 (0.78-0.95)**	**0.87 (0.79-0.96)**
Immunocompromise Category[c]					
Severe	277 (7.4)	22 (4-34)	0.93 (0.80-1.08)	0.98 (0.84-1.15)	--
Active Chemotherapy	212 (5.6)	19 (1-34)	0.98 (0.82-1.16)	--	--
High Dose Steroids	55 (1.5)	23 (6-33)	0.81 (0.59-1.12)	--	--
HIV with CD4 <200	10 (0.3)	27 (8-27)	0.72 (0.35-1.46)	--	--
Moderate	159 (4.2)	20 (8-33)	0.82 (0.67-1.01)	0.86 (0.70-1.05)	--
Solid Organ Transplant[d]	43 (1.1)	31 (14-47)	**0.60 (0.40-0.90)**	--	**0.64 (0.42-0.97)**
Chronic Biologic	23 (0.6)	30 (10-33)	0.78 (0.48-1.26)	--	--
HIV with CD4 >200	33 (0.9)	15 (6-29)	0.85 (0.56-1.29)	--	--

Other[e]	60 (1.6)	20 (8-27)	1.08 (0.78-1.50)	--	--
Immunocompetent	3322 (88.4)	16 (6-29)	Ref.	Ref.	--

Comorbidities					
Diabetes	642 (17.1)	22 (9-36)	**0.77 (0.69-0.86)**	--	**0.82 (0.73-0.93)**
Coronary Artery Disease	150 (4.0)	21 (6-40)	0.81 (0.66-1.01)	--	0.94 (0.75-1.17)
Hypertension	1120 (29.8)	21 (9-33)	**0.90 (0.82-0.98)**	--	1.07 (0.96-1.20)
ESRD	98 (2.6)	21 (13-33)	**0.76 (0.59-1.00)**	--	0.97 (0.72-1.30)
Cirrhosis	43 (1.1)	24 (1-30)	0.83 (0.57-1.20)	--	--
Obesity	1758 (46.8)	19 (7-31)	**0.89 (0.82-0.96)**	--	**0.90 (0.83-0.98)**
Chronic Lung Disease	413 (11.0)	21 (9-34)	0.91 (0.80-1.04)	--	0.94 (0.82-1.07)
Rheumatologic Disease	85 (2.3)	24 (1-36)	**0.72 (0.55-0.94)**	--	**0.75 (0.57-0.98)**
None of the above	2166 (57.6)	15 (6-28)	Ref.	Ref.	--
>=1 of the above	876 (23.3)	16 (6-29)	0.92 (0.83-1.02)	0.96 (0.86-1.06)	--
>=2 of the above	507 (13.5)	20 (9-30)	**0.84 (0.74-0.95)**	0.89 (0.77-1.02)	--
>=3 of the above	209 (5.6)	24 (10-36)	**0.68 (0.57-0.82)**	**0.73 (0.60-0.88)**	**--**

Other Conditions (in the absence of other immunocompromising conditions)					
Acute IL-6 or IL-1 Inhibitor[f]	154 (4.1)	24 (11-30)	0.87 (0.72-1.06)	--	--
Acute Corticosteroid[f]	328 (8.7)	17 (7-32.5)	0.95 (0.82-1.10)	--	--

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B-cell Function Deficiency[g]	5 (0.1)	32.5 (18-47.5)	0.60 (0.22-1.60)	--	--
Pregnant	203 (5.4)	14 (8-32)	0.90 (0.74-1.08)	--	--

Boldface indicates p value <0.05

[a] Non-parametric survival analysis accounting for interval censored-data utilizing the Expectation–Maximization-Iterative Convex Minorant

(EMICM) algorithm to impute median survival estimates and standard errors

[b] Hazard Ratios for time to SARS-CoV-2 PCR clearance obtained using Cox proportional hazards regression accounting for interval censored data,

unadjusted and adjusted for (1) age, disease severity, immunocompromise category and variables with p<0.2 in the univariate analysis and (2) age,

disease severity, and individual variables with p<0.2 in the univariate analysis

[c] Immunocompromise categories are mutually exclusive - if individuals met multiple categories, they were considered under the most severe (first

listed) category

[d] Solid organ transplant is considered under 'moderate' rather than severe as all chart-reviewed patients in this category had their transplant >1 year

prior to COVID-19 diagnosis

[e] Other immunocompromise includes: rheumatologic conditions, myelofibrosis, asplenia, chronic neutropenia, and other blood and immune disorders

(identified by ICD-10 codes on problem list), and immunocompromising medications not included in active chemotherapy category: hydroxyurea,

methotrexate, azathioprine

[f] For COVID-19 treatment; only includes individuals not otherwise categorized as immunocompromised

[g] On chronic medication which suppresses B-cell function directly or indirectly (rituximab, belimumab, natalizumab, or daratumumab) in the absence

of concurrent cytotoxic chemotherapy

Figure Legend:

Figure 1: Cycle thresholds for SARS-CoV-2 PCR tests performed in the outpatient (a, b) and inpatient setting (c, d) with available data. Grey dashed lines represent literature reported thresholds above which there is negligible likelihood of infectious virus (24 for E gene, 32 for N gene) [21,22]. Each circle represents a single test (there may be multiple tests per individual) and color corresponds to immunocompromise category (a, c) or disease severity (b, d). Mean cycle thresholds refer to mean target 1 and target 2 value within an individual test on a single assay. All assays are displayed together here except for the Abbott RealTime SARS-CoV-2 assay, which reports cycle number values that incorporate two targets into a single cycle number, which are generally lower than and not equivalent to cycle thresholds, and therefore are displayed separately in the supplemental figure.