Review

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Prognostic value of anti-SARS-CoV-2 antibodies: a systematic review

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Abstract

Objectives: Globally, over 772 million cases of COVID-19 have been reported. New variants of interest with corresponding spikes in case numbers continue to be identified. Vulnerable patients, including older adults or patients with severe comorbidities, continue to be at risk. A large body of evidence has been accumulated regarding anti-SARS-CoV-2-antibodies and COVID-19 but the usefulness of antibody measurements remains unclear. This systematic review aims to assess the prognostic value of anti-SARS-CoV-2-antibodies and their usefulness for guiding booster vaccinations.

Methods: Studies in English and published between January 2020 and October 2023 were included. Studies that relied on multiparameter-models or comprised fewer than 100 participants were excluded. PubMed and via the WHO COVID-19 research database, Embase and Medline databases were searched. Study selection and quality assessment was conducted independently by two researchers.

Results: After screening 1,160 studies, 33 studies comprising >30 million individuals were included. Anti-SARS-CoV-2-antibodies were strongly associated with reduced risk of SARS-CoV-2-infection and better outcomes, including mortality. Risk of infection and COVID-19 severity decreased with increasing antibody levels.

Conclusions: Anti-SARS-CoV-2-antibodies are useful for early identification of high-risk patients and timely adjustment of therapy. Protective thresholds may be applied to advise booster vaccinations but verification in separate cohorts is required.

Keywords: COVID-19; anti-SARS-CoV-2 antibodies; correlate of protection; spike; nucleocapsid; neutralizing antibodies

Introduction

Globally, more than 772 million confirmed cases of COVID-19 have been reported to the World Health Organization [1]. Although testing for SARS-CoV-2 infections has substantially declined [2] and infection numbers are no longer reported in detail, new variants of interest (VOI) with corresponding spikes in case numbers continue to be registered [3]. The latest two VOI include EG.5, a sublineage of XBB.1.9.2, that has led to a global increase in case numbers [4] and currently accounts for approximately 52 % of global SARS-CoV-2 variant proportions, and BA2.86, a variant that was first assessed by the World Health Organization (WHO) in November 2023, and has since steadily grown from a global proportion of 1.8–8.9 % [5].

Vulnerable patient subsets, such as older adults, obese patients or patients with multiple or severe comorbidities have exhibited the highest infection fatality rates throughout the pandemic and continue to be at risk from the currently prevailing and comparatively milder Omicron variant [6–10].

Global vaccination programs have played a major part in curbing mortality rates and reducing the risk of adverse outcomes [11–15]. However, current recommendations on booster vaccinations are broad [16] and may be insufficient for patients with additional risk factors or for older adults who are known to have reduced quality, strength and durability of vaccine-induced antibody responses [17–22].

While a large body of evidence has been accumulated regarding COVID-19, data on the usefulness of antibody measurements is conflicting. In order to best protect vulnerable patients and enable informed decisions on the timing of booster vaccinations, it is necessary to understand if and to what extent anti-SARS-CoV-2 antibodies

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confer protection against SARS-CoV-2 infection and severe COVID-19, including COVID-19 related mortality.

This systematic review therefore aims to evaluate the prognostic value of anti-SARS-CoV-2 antibodies for identifying patients at high risk of adverse outcomes in a clinical setting and their potential usefulness as a correlate of protection for guiding future booster vaccinations.

Methods

Search methods and study selection

This systematic review was conducted according to PRISMA guidelines [23]. The PubMed database was searched on November 6, 2023 using the following search terms: ((“COVID-19” [Title/Abstract] OR “SARS-CoV-2” [Title/Abstract]) AND (antibodies [Title/Abstract] OR antibody [Title/Abstract] OR vaccine [Title/Abstract])) AND (outcome [Title/Abstract] OR severity [Title/Abstract] OR mortality [Title/Abstract] OR prognosis [Title/Abstract]) while filtering for human probands and publications in English.

The WHO COVID-19 research database [24] was searched on December 1, 2023 using the search terms “prognosis OR mortality OR severity OR outcome” while filtering for publications from MEDLINE and EMBASE, and publications in English. The complete search was defined as follows: “prognosis OR mortality OR severity OR outcome AND db: (“MEDLINE” OR “EMBASE”) AND mj: (“Antibodies, Viral” OR “Antibodies, Neutralizing”) AND type_of_study: (“prognostic_studies” OR “observational_studies” OR “experimental_studies” OR “cohort_studies” OR “rct” OR “diagnostic_studies”) AND la: (“en”)”.

To widen our search, references of included manuscripts were also screened for relevant studies. Peer reviewed observational studies, case control studies, clinical trials and randomized controlled trials published between January 2020 and October 2023 were eligible for inclusion.

Studies not pertinent to our review question were excluded. Thus, studies that did not examine the prognostic value of antibody measurements either preceding COVID-19 or at the onset of COVID-19 infection but focused on antibody kinetics following COVID-19 were excluded. Studies that relied on multiparameter models to predict prognosis and studies that comprised fewer than 100 participants were also excluded. We further excluded studies not written in English, preprints, letters to the editor and short communications and studies without available full text.

Literature screening and data analysis

The Rayyan platform for systematic reviews [25] was used to organize studies and conduct the screening process. After removal of duplicates, title and abstract were screened independently by SM and PR. Full text screening and data extraction were also performed independently by both SM and PR. Conflicts were resolved through discussion.

We collected data on study characteristics, year of publication, journal, author, study cohort, type of antibody measured, outcome, and study results. Data was sought on the following outcomes – immunity against COVID-19 infections and COVID-19 severity.

Risk assessment for bias of cohort studies was conducted independently by SM and PR using the respective Critical Appraisal Skills Programme (CASP) Checklist for cohort studies and case control studies [26, 27]. Randomized controlled trials were assessed with the Cochrane Risk of Bias (ROB) 2.0 Tool [28]. Due to the high heterogeneity of the included studies, the high variability in reported risk measures, and the fact that several studies did not provide any risk measures, conducting sensitivity analyses or a metaanalysis was not considered feasible.

Results

A total of 1,160 eligible studies were identified from PubMed and via the WHO COVID-19 research database, from Embase and Medline databases. After removal of duplicates, 1,113 articles were screened, of which 84 were retrieved. Full text perusal yielded 33 studies that met the inclusion criteria. Figure 1 outlines the process of study identification and selection.

We identified 11 studies that evaluated the role of anti-SARS-CoV-2 antibodies in the prevention of reinfection or breakthrough infections, 20 studies that focused on the association between preexisting antibody levels and disease severity and 2 studies that gave results on both aspects. Data on the latter two studies will be reported both for the association of antibodies with immunity and for the association of antibodies with COVID-19 severity. With regard to studies on the conferral of immunity against COVID-19, two phase 3 clinical trials, 3 retrospective and 8 prospective cohorts were included. Studies on the association between antibodies and COVID-19 severity comprised 16 prospective and 6 retrospective cohorts. Table 1 summarizes the included studies regarding anti-SARS-CoV-2 antibodies and immunity against SARS-CoV-2 infection and Table 2 lists included studies pertaining to anti-SARS-CoV-2 antibodies and COVID-19 severity.

In total, 30,443,905 individuals were included, of which 30,432,941 pertained to studies on immunity and 14,701 to studies on COVID-19 severity. Observed heterogeneity among studies was high, with a wide variety of antibody types, antibody testing systems, and outcomes. Evaluated antibody types comprised neutralizing antibodies, anti-SARS-CoV-2 spike antibodies, anti-RBD antibodies and anti-nucleocapsid antibodies. Severity outcomes included symptomatic infections, hospitalization, oxygen administration, invasive ventilation, development of pneumonia, ICU admission, mortality, in-hospital mortality and 28-day mortality. Similarly to outcomes, reported risk measures were highly heterogeneous, and not provided in 15 of 33 studies.

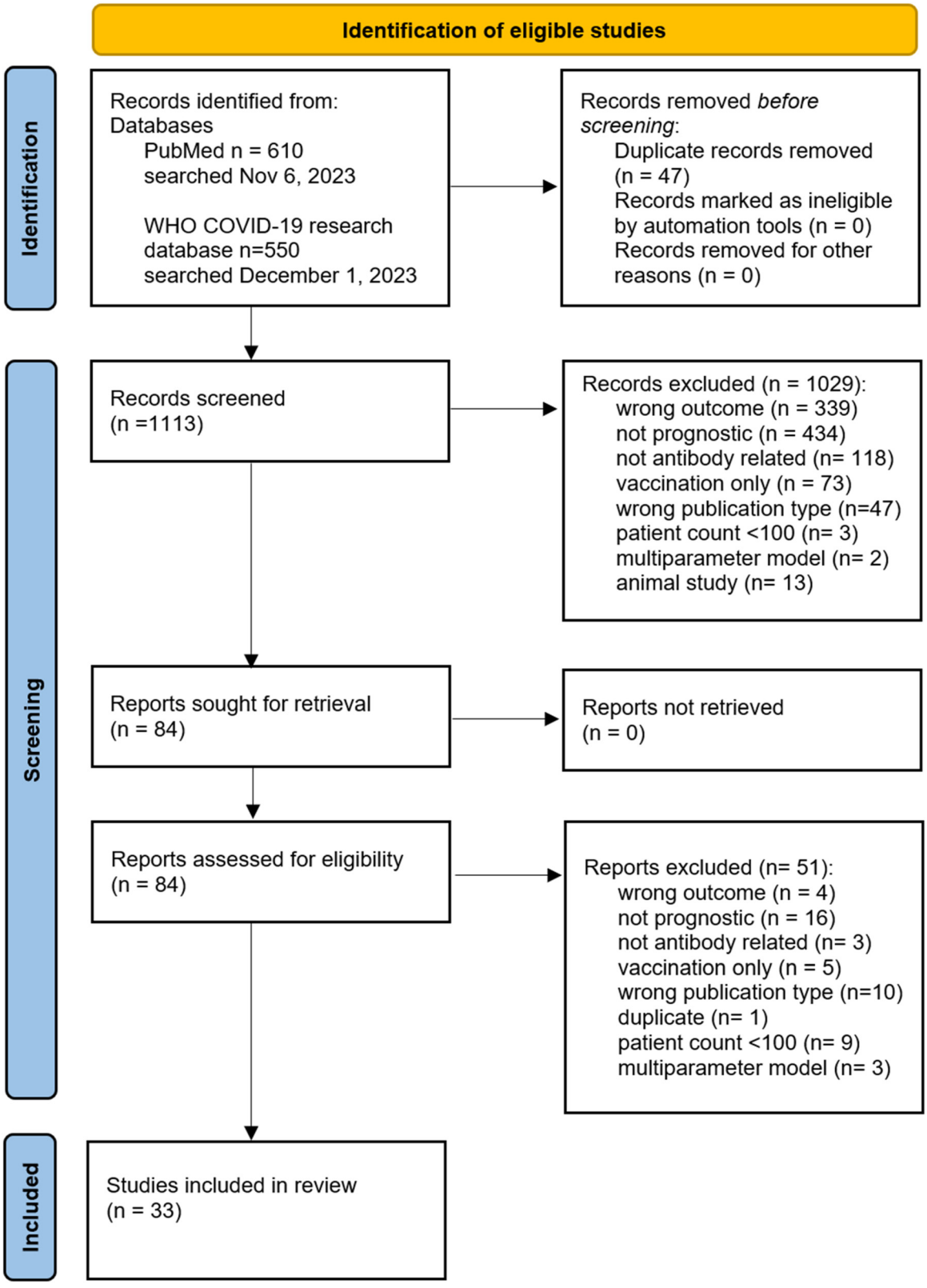

Figure 1: PRISMA 2020 flow chart for study selection.

Table 1: Included studies regarding the association of anti-SARS-CoV-2 antibody levels with immunity against SARS-CoV-2 infection sorted by patient count.

First author, country	Year	n	Study type	Study population	Antibody type	Antibody assay	Outcome	Main result	Potential sources of bias	Score
Reynolds [29], U.S.	2023	27,070,023	Retrospective cohort	General	Not specified	Not specified	Reinfection	87 % lower risk of reinfection among index-positive than index-negative individuals	Retrospective analysis; antibody assays not specified	High
Harvey [30], U.S.	2021	3,257,478	Retrospective cohort	General	Not specified, >91 % IgG	Not specified	Reinfection	Seropositivity is associated with protection from infection.	Retrospective analysis; serological assays not specified	High
Fong [31], U.S.	2022	44,325	Phase 3 clinical trial; immunogenicity cohort	Adults	ID50; spike, RBD IgG	Pseudo-virus neutralization; ECLIA	Breakthrough infection	COVID-19 risk decreased with increasing antibody marker tertile; significant for ID50, not for spike and RBD antibodies	Spike and RBD antibody ranges may have been too low to detect significant differences	Moderate
Hall [32], U.K.	2021	25,661	Prospective cohort	Healthcare workers	Not specified	Not specified	Reinfection	Patients with antibodies from previous infections are less likely to be reinfected	may be subject to some recall bias; serological assays not specified	High
Gilbert [33], U.S.	2022	14,064	Phase 3 clinical trial; cohort vaccine recipients	Adults	RBD, spike IgG	ECLIA	Breakthrough infection	COVID-19 risk of vaccine recipients decreases as antibody marker levels increase	Relatively short follow-up time of 4 months	High
Lumley [34], U.K.	2021	12,541	Prospective cohort	Healthcare workers	Spike, nucleocapsid IgG	ELISA, CLIA	Reinfection	The presence of antibodies was associated with a substantially reduced risk of reinfection in the ensuing 6 months	may be subject to some selection bias	High
Quiroga [35], Spain[a]	2023	2,186	Prospective cohort	Chronic kidney disease	Spike IgG	CLIA	Breakthrough infection	Admission for breakthrough COVID-19 was associated with low anti-spike antibody titers.	Underlying therapy may limit generalisability to other countries	High
Havervall [36], Sweden	2021	1935	Prospective cohort	Adults	Spike IgG	Bead-based multiplex assay	Reinfection	The presence of anti-spike IgG antibodies is associated with a substantially reduced risk of reinfection up to 9 months following asymptomatic to mild COVID-19.	Low chance of recall bias	High
Jeffery-Smith [37], U.K.	2021	1,625	Prospective cohort	Care home residents	Spike, nucleocapsid IgG; neutralizing antibodies	ELISA, CLIA; live virus neutralization	Breakthrough infection	Reinfection was associated with no or low neutralising antibody before reinfection	Potentially some bias from comparing older residents to younger, healthier staff	High
Pinana [38], Spain[a]	2023	1,551	Prospective cohort	Hematological patients	Nucleocapsid IgG, spike IgG	ELISA, CLIA	Breakthrough infection	A serological cut-off of 250 BAU/mL was able to discriminate the risk of being infected and the disease severity	may not be generalisable to patients on different treatment regimes; used different testing systems at different test centers	High

Table 1: (continued)

First author, country	Year	n	Study type	Study population	Antibody type	Antibody assay	Outcome	Main result	Potential sources of bias	Score
Liu [39], U.K.	2023	1,228	Prospective cohort	Inflammatory bowel disease	Neutralizing antibodies	Pseudo-virus neutralization assay	Breakthrough infection	Higher antibodies associated with lower HR and hence longer time to breakthrough infection	may not be generalisable to patients on different treatment regimes	High
Jeffery-Smith [40], U.K.	2021	209	Prospective cohort	Care home residents	RBD, nucleocapsid IgG	EIA	Reinfection	Only 1.1 % of seropositive vs. 24.7 % of seronegative patients were reinfected	Potentially some bias from comparing older residents to younger, healthier staff	High
Wand [41], Israel	2022	115	Retrospective cohort	Hemodialysis	Spike IgG	CMIA	Breakthrough infection	Patients with <50 AU/mL had 5.8 times higher odds of infection	Retrospective analysis; low patient number	High

[a]Studies that included information on both immunity and COVID-19 severity and were thus included in both listings. AU antibody unit, BAU, binding antibody unit; COVID-19, coronavirus disease 2019; CLIA, chemiluminescent immunoassay; CMIA, chemiluminescent microparticle immunoassay; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; RBD, receptor binding domain; ICU, intensive care unit.

Quality assessment scores based on CASP checklists were divided in thirds to discriminate low, moderate and high quality scores. Of 33 included studies, 2 ranked in the low category, 6 in the moderate and 25 in the high category. Potential sources of bias are listed in Table 1. Figure 2 illustrates details on study origin, patient cohorts, outcomes, measured antibody types and quality scores.

Antibodies and immunity against SARS-CoV-2 infection

All of 13 identified studies regarding immunity against SARS-CoV-2 reported an association between anti-SARS-CoV-2 antibodies and reduced rates of reinfection or breakthrough infections.

Seropositivity

A large retrospective study from the U.S. analysing data from over 27 million patients calculated that risk of reinfection was substantially reduced in antibody positive individuals compared to antibody negative individuals (HR 0.13, 95 % CI 0.13–0.13) for a duration of at least 5 months and up to one year after primary infection [29]. These results are substantiated by a further study comprising over 3 million individuals that found seropositivity to be associated with protection from reinfection [30]. Two comparatively large studies on British healthcare workers report concordant results [32, 34]. Firstly, a multicenter study that included 25,661 participants from publicly funded hospitals found that individuals with antibodies from previous infections were less likely to have a reinfection [32]. Secondly, a British study on 12,541 healthcare workers stated that the presence of anti-spike IgG antibodies markedly reduced the risk of reinfection in the ensuing 6 months with an adjusted incidence rate ratio of 0.11 (95 % CI 0.03–0.44) [34]. Similar results were obtained by a Swedish study comprising 1,935 adults that purported reduced risks of reinfection for up to 9 months in IgG positive individuals, with a protective effect of 95.2 % (95 % CI 81.9–99.1 %) [36]. A smaller study of 209 care home residents also reports concordant results [40].

Antibody levels

In addition, antibody levels were found to be significantly lower in patients who experienced reinfection or breakthrough infections than in those who did not [35, 37]. Several studies further suggest that higher antibody levels correlate with longer time to breakthrough infection [39] and that

Table 2: Included studies regarding the association of anti-SARS-CoV-2 antibody levels with COVID-19 severity, sorted by patient count.

First author, country	Year	n	Study type	Study population	Antibody type	Antibody assay	Outcome	Main result	Potential sources of bias	Score
Feng [42], U.K.	2021	4,372	Prospective cohort	ChAdOx1 nCoV-19 correlates population	Spike, RBD IgG	Not specified	Symptomatic infection	The risk of symptomatic COVID-19 decreased with increasing antibody levels	Soft endpoint that may be subject to assessment bias	High
Quiroga [35], Spain[a]	2023	2,186	Prospective cohort	Chronic kidney disease	Spike IgG	CLIA	Hospital admission	Admitted patients had prior titers <620 IU/mL and lower median values than non-admitted patients	Underlying therapy may limit generalisability to other countries	High
Pinana [38], Spain[a]	2023	1,551	Prospective cohort	Hematological patients	Nucleocapsid IgG, spike IgG	ELISA, CLIA	Symptomatic infection, pneumonia, hospitalization, oxygen, mortality	A serological cut-off value of 250 BAU/mL was able to discriminate the risk of being infected and the disease severity	Except for mortality soft endpoints which may be subject to assessment bias; used different testing systems at different test centers	High
Mink [43], Austria	2023	1,152	Prospective cohort	Hospitalized patients	Spike IgG	Immunoassay	In-hospital mortality	Antibody levels at hospital admission are inversely associated with mortality. Patients infected with the omicron variant were 4 times more likely to die if antibodies were <1,200 U/mL	Limited to hospitalized patients	High
Mink [44], Austria	2023	1,046	Prospective cohort	Type 2 diabetes (T2D)	Spike IgG	Immunoassay	Mortality, ICU admission, oxygen administration	Mortality risk increased two-fold with each standard deviation-decrease of antibody levels; T2D patients requiring oxygen administration, intubation and ICU admission had significantly lower antibody levels than those who did not	Limited to hospitalized patients	High
Sananez [45], Argentina	2021	730	Prospective cohort	Hospitalized children	Spike IgM and IgG	ELISA	Severe COVID-19	Severe COVID-19 in children is associated with a defective antibody response during acute infection	may be subject to some assessment bias; comprised different patient groups, not all with acute infection	Moderate
Sanghavi [46], U.S.	2022	627	Retrospective cohort	Hospitalized patients	Spike IgG	Immuno-assay	ICU admission, mortality	In breakthrough cases, low-titer patients had higher need for ICU care and higher mortality than high-titer patients (>132 U/mL).	may be subject to some assessment bias regarding ICU admission	High
Sulaiman [47], U.S.	2021	589	Prospective cohort	Critically ill adults	Spike + RBD IgG, IgM and IgA	Not specified	Mortality	Antibody levels were significantly lower in the deceased group as compared patients who survived	may be subject to some selection bias; bronchoalveolar lavage sample material	High
Yang [48], China	2022	580	Retrospective cohort	Hospitalized patients	Spike IgG	CMIA	Severe COVID-19	Compared with the unvaccinated group, the vac + IgG + group had a 0.05 (0–0.63)-fold risk of suffering from severe cases.	Retrospective analysis; may be subject to some assessment bias	High

Table 2: (continued)

First author, country	Year	n	Study type	Study population	Antibody type	Antibody assay	Outcome	Main result	Potential sources of bias	Score
Secchi [49], Italy	2020	509	Prospective cohort	Hospitalized patients	RBD IgG	LIPS	Mortality	The development of SARS-CoV-2 RBD IgG antibodies was associated with improved patient survival	did not adjust for all potential confounders (e.g. BMI)	High
Ruytinx [50], Belgium	2023	434	Retrospective cohort	Hospitalized patients	S1 IgM, IgG	ELISA	Hospital mortality	Increased baseline antibody response was associated with decreased odds for hospital mortality.	Retrospective analysis	High
Paggi [51], Italy	2023	420	Retrospective cohort	Vaccinated hospitalized patients	Spike IgG	Not specified	Mortality	Vaccinated seronegative patients' in-hospital mortality was significantly higher than vaccinated seropositive patients	Retrospective; time of antibody measurement not given	Moderate
Bernal [52], Spain	2023	232	Prospective cohort	Hospitalized patients	Spike IgG	CMIA	Mortality, ventilation	Vaccination but not antibody titers protected from adverse events	Composite endpoint of ventilation and death;	Low
Lucas [53], U.S.	2021	229	Prospective cohort	Adults	Neutralizing anti-bodies	Not specified	Mortality	Delayed antibody production in lethal COVID-19; early neutralizing antibodies correlate with COVID-19 recovery	May be subject to some selection bias; details for antibody assay not specified	High
Klineova [54], U.S.	2023	209	Prospective cohort	MS, MS related	Spike IgG	Various	Hospitalization	Postvaccination antibody response was not associated with hospitalization risk	Different antibody assays, antibody levels only available in 79 patients; threshold may have been too low	Low
Dispinseri [55], Italy	2021	162	Prospective cohort	Hospitalized patients	Neutralizing anti-bodies	Pseudo-virus neutralization	Mortality	The lack of neutralizing capacity correlates with an increased risk of a fatal outcome.	Comparatively low patient count	High
Al-Muhaiteeb [56], Kuwait	2022	138	Prospective cohort	Hemodialysis	Spike IgG	CLIA	Hospitalization	Hospitalized patients had lower antibody titers than those who were not hospitalized	In addition to PCR tests, antigen self tests were admissible as proof of infection	Moderate
Nagura-Ikeda [57], Japan	2021	130	Retrospective cohort	Hospitalized patients	Spike total and IgG	CLIA	Severity (clinical symptoms of pneumonia)	Prevalence or concentration of total or IgG antibody on admission were not associated with disease prognosis	Low patient count with positive IgG antibodies on admission; assessment bias due to soft endpoint; retrospective analysis	Moderate
Yang [58], U.S.	2021	120	Retrospective cohort	Hospitalized patients	RBD total	Bio-sensor assay	Mortality	Total antibody positivity rate at hospital admission was significantly higher for the patients who survived than for patients who died	Retrospective analysis; not all potential confounders were taken into account	High
Malahe [59], Netherlands	2023	114	Prospective cohort	Immuno-compromised	Spike IgG	CLIA	Hospitalization	A low SARS-CoV-2 antibody response (<300 BAU/mL) at diagnosis were associated with hospital admission	Retrospective; different adjustment models – not all potential confounders were included in 1 model	High

Table 2: (continued)

First author, country	Year	n	Study type	Study population	Antibody type	Antibody assay	Outcome	Main result	Potential sources of bias	Score
Shrivastava [60], India	2021	109	Prospective cohort	Hospitalized patients	Neutralizing anti-bodies	Plaque reduction neutralization test	Severe disease (ICU + oxygen saturation <93 % at ambient air)	Seropositivity in severe disease patients was higher than in mild disease and asymptomatic categories.	Healthcare access not equal in India – potential selection bias; outcome is subject to some assessment bias	Moderate
Lerum [61], Norway	2021	108	Prospective cohort	Hospitalized patients	RBD IgG	Multiplexed bead-based flow cytometric assay	Poor pulmonary outcome	Low antibody levels at admission were predictors of poorer pulmonary outcome after 3 months.	Adjusted for age, sex, treatment, and smoking but not BMI	High

[a]Studies that included information on both immunity and COVID-19 severity and were thus included in both Tables 1 and 2. BAU, binding antibody unit; COVID-19, coronavirus disease 2019; CLIA, chemiluminescent immunoassay; CMIA, chemiluminescent microparticle immunoassay; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; LIPS, luciferase immune precipitation; RBD, receptor binding domain; ICU, intensive care unit; MS, multiple sclerosis.

post-vaccination COVID-19 risk decreases as antibody levels increase [33]. Accordingly, a study on 1,551 hematological patients reported that a serological titer of less than 250 BAU/mL of anti-SARS-CoV-2 spike antibodies was predictive of breakthrough infection and its severity [38].

Conflicting evidence

One study found an association between ID 50 titers from a pseudovirus neutralization assay and occurrence of breakthrough infection but could not confirm this association for spike and RBD antibodies. However, these results may have been affected by the relatively low antibody thresholds used for the latter tests, which classified patients with more than 59 BAU/mL as having high antibody levels [31].

Antibodies and COVID-19 severity

18 of 22 identified studies reported an association between antibody levels prior to or at the onset of COVID-19 infection and ensuing COVID-19 severity. Severity measures were highly heterogeneous, ranging from symptomatic infection to hospitalization, pneumonia, ICU admission and death. Figure 2I summarizes the different outcomes. Several studies examined more than one severity measure.

Symptomatic infection

A study published in Nature Medicine examining vaccine efficacy in 4,372 individuals reported 90 % vaccine efficacy at 899 BAU/mL for anti-spike IgG as well as decreasing risk of symptomatic COVID-19 with increasing levels of anti-spike and anti-RBD antibodies [42].

Hospitalization

In 2,186 patients with chronic kidney disease from Spain, patients who were admitted to the hospital had prior anti-spike antibody titers below 620 IU/mL and lower median values than patients who were not hospitalized [35]. These data are supported by a smaller study of 114 immunocompromised patients infected with the Omicron variant that found higher anti-spike antibody levels (>300 BAU/mL) at the time of diagnosis were associated with reduced risk of hospital admission (OR 0.053, 95 % CI 0.006–0.44, p=0.006) [59]. Another prospective cohort study from Spain on 1,551 hematological patients further reported that antibody levels below 250 BAU/mL were associated with higher risk

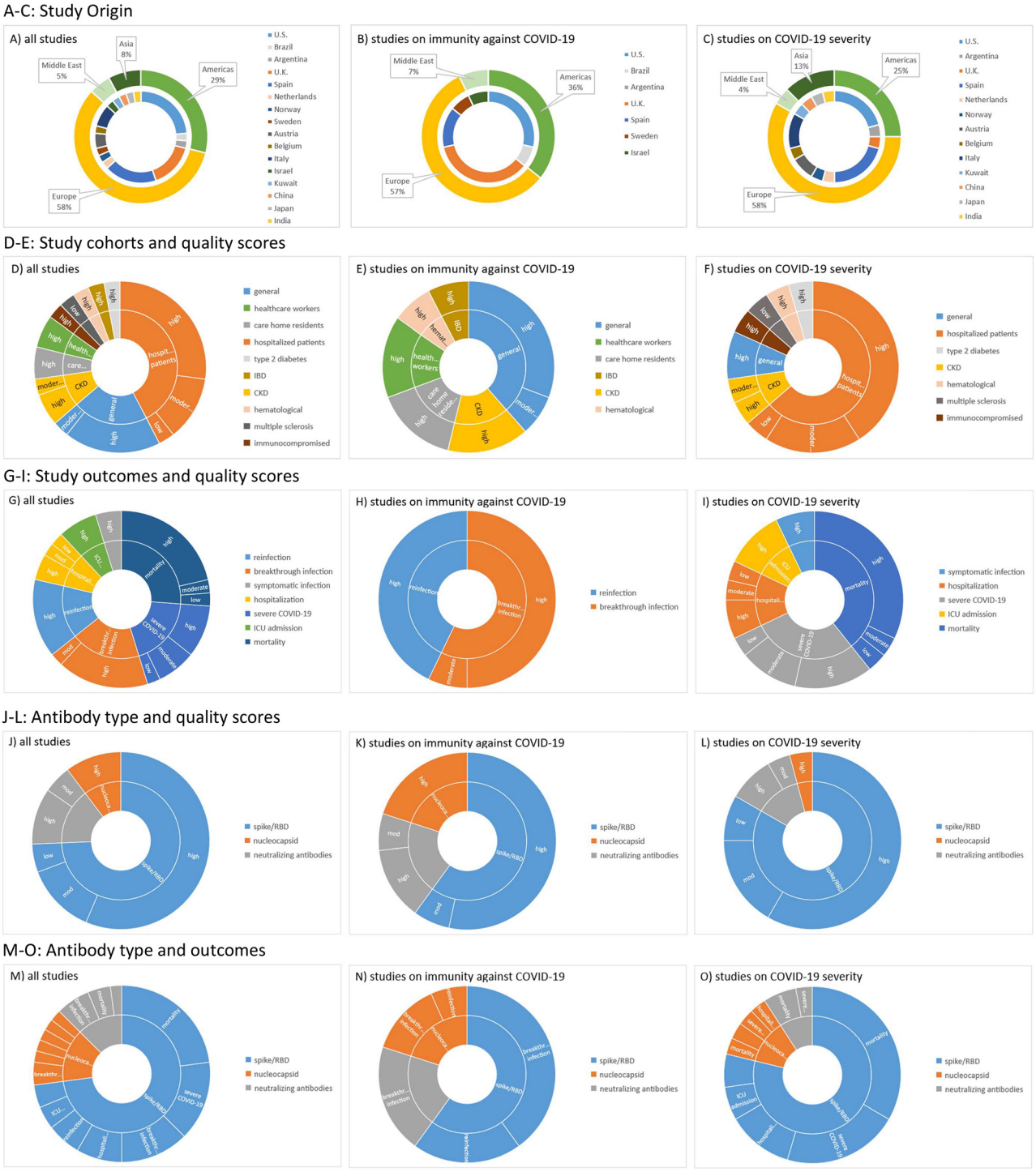

Figure 2: Study characteristics. (A) Origin of studies on prognostic value of anti-SARS-CoV-2 antibodies in COVID-19, (B) origin of studies on anti-SARS-CoV-2 antibodies and immunity against SARS-CoV-2 infection, (C) origin of studies on anti-SARS-CoV-2 antibodies and COVID-19 severity. (D) Study cohorts and quality scores (low/moderate/high) of studies on prognostic value of anti-SARS-CoV-2 antibodies in COVID-19, (E) study cohorts and quality scores for studies on immunity against COVID-19, (F) study cohorts and quality scores for studies on COVID-19 severity; (G) study outcomes with quality scores of studies on prognostic value of anti-SARS-CoV-2 antibodies in COVID-19, (H) study outcomes with quality scores for studies on immunity against COVID-19, (I) study outcomes with quality scores for studies on COVID-19 severity. (J) Antibody type and quality scores of studies on prognostic value of anti-SARS-CoV-2 antibodies in COVID-19, (K) antibody type and quality scores of studies on immunity against COVID-19, (L) antibody type and quality scores of studies on COVID-19 severity. (M) Antibody type and outcome of studies on prognostic value of anti-SARS-CoV-2 antibodies in COVID-19, (N) antibody type and outcome of studies on immunity against COVID-19, (O) antibody type and outcome of studies on COVID-19 severity. Studies with multiple outcomes or antibody types were counted in each category.

of symptomatic SARS-CoV-2 infection, pneumonia, hospital admission, oxygen requirement and death [38].

Severe COVID-19

Several medium sized studies also report an association between lower antibody levels and elevated risks of severe COVID-19. In a cohort of 730 hospitalized children from Argentina of which 550 had an acute SARS-CoV-2 infection, low antibody concentrations within 4 days of hospital admission were associated with severe COVID-19, characterized by pneumonia, respiratory distress, lethargy and convulsions [45]. In addition, a retrospective Chinese study examining anti-spike IgG on hospital admission of 580 patients noted that, in comparison to unvaccinated patients, vaccinated seropositive patients had adjusted odds ratios of 0.05 (95 % CI 0–0.63) to 0.14 (95 % CI 0.02–0.87) for developing severe COVID-19 pneumonia depending on the adjustment model [48]. Accordingly, in a Norwegian study, low antibody levels at hospital admission were associated with poorer pulmonary outcome after three months [61].

Moreover, a prospective multicenter cohort study on 275 patients with type 2 diabetes (T2D) noted that patients who required oxygen administration, endotracheal intubation and ICU admission had significantly lower anti-SARS-CoV-2 spike antibodies on hospital admission than patients who did not [44]. With regard to ICU admission, a retrospective study on 627 hospitalized patients further reported that low-titer patients (<132 U/mL) had higher need for ICU care (24 [51.1 %] vs. 22 [11.0 %], p=0.034) than high-titer patients (>132 U/mL) in breakthrough cases [46].

Mortality

In a prospective multicenter cohort study on 1,152 hospitalized COVID-19 patients, anti-SARS-CoV-2 spike antibodies measured on admission were inversely associated with in-hospital mortality. In patients infected with the Omicron variant, mortality risk was 4 times higher if antibody levels were below 1,200 BAU/mL (aOR 4.08, 95 % CI 1.81–9.20, p<0.001) [43].

Further, in T2D patients, mortality risk increased two-fold with each standard deviation decrease of antibody levels (aHR 1.99, 95 % CI 1.23–3.22, p=0.005). Comparable results were observed for the control group of 877 non-diabetic individuals [44].

This is supported by another study comprising 589 critically ill adults from the U.S. that found IgG levels of anti-spike and anti-RBD antibodies were significantly lower in the deceased group as compared to the levels found in patients who survived [47]. A retrospective study of 627 hospitalized U.S. patients further reported that low-titer patients had higher mortality (10 [21.3 %] vs. 5 [6.8 %], p=0.025) than high-titer patients (>132 U/mL)[46].

Accordingly, another retrospective cohort study of 434 hospitalized patients described lower odds of in-hospital mortality for patients with higher baseline anti-spike antibody levels [50]. A smaller study from Italy including 152 vaccinated patients with anti-spike IgG measurements also found significantly lower mortality in seropositive vs. seronegative patients (10.7 vs. 33.3 %, p=0.005)[51]. Similar results were obtained by four other medium sized studies comprising between 120 and 509 patients that reported an association between antibody levels and lower mortality [49, 53, 55, 58].

Conflicting evidence regarding hospitalization and severe disease

In contrast to the above, we identified four smaller studies that could not confirm an association between antibody levels and COVID-19 severity [52, 54, 57, 60]. Participant counts ranged from a total of 109–232 individuals, however the number of antibody positive patients was below 100 in each study, with one study [57] comprising only 34 seropositive individuals. Of note, due to various potential sources of bias, these studies were either graded in the lowest or in the moderate scoring tertile according to the CASP checklist (compare Table 1).

One study examining multiple sclerosis patients did not find an association between antibody levels and hospitalization. However, the results of this study may have been affected by several potential sources of bias. Firstly, antibody measurements were only available for 79 of 209 patients, suggesting a potential selection bias. Secondly, antibody measurements were conducted using more than one assay and thirdly, the time of measurement spanned a period of 6 months preceding infection, which may have introduced assessment bias [54].

Another study analyzing 232 hospitalized patients, of whom 91 were seropositive for anti-spike antibodies, did not find an association between antibody titers and the composite outcome of ventilation and death [52]. The composite endpoint of these two outcomes may have resulted in some degree of assessment bias.

Finally, a small study from India comprising 109 hospitalized patients, of whom antibody measurements were conducted in 82 patients, could not confirm an association between neutralizing antibodies and development of severe disease as defined by ICU admission and reduced oxygen saturation at ambient air [60]. Apart from the low patient count, unequal healthcare access in India may have

resulted in some degree of selection bias. In addition, the study was conducted between April and June 2020 when vaccines were not yet available, suggesting that the antibody response measured in this population was formed entirely in response to the infection present at the time of the study.

Discussion

In this systematic review that included 33 studies and over 30 million individuals, we found that anti-SARS-CoV-2 antibodies were consistently associated with reduced risk of reinfection or breakthrough infection for 5–12 months after primary infection and for at least 4 months after vaccination. With regard to anti-SARS-CoV-2 antibody levels and reduced COVID-19 severity, the overwhelming majority of identified studies observed significantly better outcomes in seropositive vs. seronegative patients. We further found that both risk of infection and COVID-19 severity decreased with increasing antibody levels.

Interpretation

These results are in accordance with evidence from large vaccine efficacy studies that did not report antibody measurements. For instance, a study comprising over 4.5 million individuals from Israel aged 16 years or older noted that rates of confirmed infection were approximately 10 times lower after booster vaccination than in non-boostered individuals [12]. In boostered patients aged 60 years or older, rates of severe illness and mortality were 17.9 (95 % CI 15.1–21.2) and 14.7 (95 % CI 10.0–21.4) times lower after booster vaccination. Accordingly, a study including 1.2 million older adults showed that a fourth dose lowered rates of severe COVID-19 by a factor of 3.5 (95 % CI 2.7–4.6) [13]. A meta-analysis of 10 studies encompassing close to 10 million individuals also showed that primary infection was associated with a weighted average risk reduction of 90.4 % for reinfection (standard deviation 7.7 %, $p<0.01$) [62].

In line with results from this systematic review, previous studies show that risk of SARS-CoV-2 infection was reduced following vaccination or preceding infection but protection was not absolute and the duration was relatively short lived [12, 62]. In contrast, protection against adverse outcomes appeared to last longer [12] and lower antibody levels were sufficient to confer protection [63].

While included studies primarily reported anti-SARS-CoV-2 spike and/or RBD antibody levels, these antibodies have been shown to correlate well with neutralizing potency and therefore constitute a good surrogate for measuring neutralizing antibodies [55, 64].

This systematic review found similar results by studies conducted at the beginning of the pandemic, when Alpha and Delta variants were prevalent, and more recent studies based on infections with the Omicron variant, suggesting that antibody measurements are useful as a prognostic tool irrespective of the prevailing virus variant. However, antibodies formed against wild-type SARS-CoV-2 have been shown to lose some neutralizing potency against the Omicron variant [65, 66]. While, sufficiently high antibody levels were still found to be protective, this suggests that not all antibody levels are equally efficient and that regular booster vaccinations with updated vaccines are required in order to best protect vulnerable patient groups. In addition, antibody levels decline more quickly in older adults [17–22] and antibody affinity is known to decrease with age due to a combination of factors including reduced somatic hypermutation and lower rates of spontaneous mutations in variable regions [67, 68]. Hence, antibody thresholds for guiding booster vaccinations need to be set high enough to account for this variability in efficiency.

Importantly, antibody levels that are present at the onset of an infection seem to confer protection against severe courses and COVID-19 related mortality and may thus be useful for early identification of high-risk patients and timely adjustment of therapy. However, as severe courses elicit stronger antibody responses than mild disease, antibody levels measured in the course of COVID-19 are no longer indicative of protection but appear to reflect the current disease severity [53, 69–72]. Thus, the prognostic usefulness of anti-SARS-CoV-2 antibodies depends on the time of measurement.

Limitations of included evidence

A high degree of heterogeneity was present among the studies that were included in this systematic review. Sources of heterogeneity included different antibody testing systems, different antibody types, a wide range in the timing of antibody measurements, different follow up periods and different severity measures. Risk measures were also highly heterogeneous and only reported in a fraction of studies.

Although the number of studies included with regard to immunity against SARS-CoV-2 and COVID-19 severity were similar, the total number of included individuals was substantially lower for studies on COVID-19 severity (30,432,941 vs. 14,701).

All currently available evidence is based on observational cohort studies. Two studies were classified as phase 3 clinical trials; however, the antibody analysis conducted by these studies was based on a cohort and is thus also observational in character. The presence of some degree of reporting bias cannot be excluded, particularly with regard to immunity against SARS-CoV-2 infection as no studies reporting negative results could be identified.

Included studies consistently reported an inverse association between higher antibody levels and reduced rates of infection or reinfection, as well as between higher antibody levels and lower rates of symptomatic infection and COVID-19 mortality. However, while several larger and medium-sized studies also observed reduced rates of hospitalisation and severe courses, there was some conflicting evidence from four smaller studies with regard to the latter two outcomes.

Differences in study results may stem from various factors, most notably low patient count and wide ranges in the timing of antibody measurements. In addition, studies based on softer endpoints such as disease severity depend on subjective clinical assessments and are thus more prone to assessment bias than studies based on hard endpoints like patient mortality [73].

Vaccination status may also affect results as studies conducted during the early phases of the pandemic primarily included non-vaccinated patients without previous SARS-CoV-2 contact, whose antibody levels were solely formed in response to the present infection and hence not indicative of pre-existing protection.

In addition, current evidence shows that protection against infection and adverse outcomes increases incrementally with higher antibody levels [33, 44]. Accordingly, several studies that have found better outcomes with higher antibody levels have suggested relatively high antibody thresholds [35, 42, 43]. Thus, studies employing very low thresholds may have been unable to detect a potential protective effect because antibody levels were insufficient.

Several studies that were included in this systematic review did not provide details on the antibody assays that were used in their work. For instance, a large, comprehensive study on more than 27 million individuals by Reynolds et al. [29], only reported that anti-SARS-CoV-2 antibodies were measured but did not describe the assays that were employed by the respective study centres.

In addition, while some studies did report binding antibody units (BAU), it has to be noted that, contrary to the original intention of introducing this unit, significant differences have been described between assays and a complete harmonization of test results has not yet been achieved [74]. While the variability between different assays is unlikely to affect the overall outcome of the studies included in this systematic review, it may limit the comparability between studies and compound the challenge of defining protective antibody thresholds.

Strengths and limitations of the review process

We conducted a comprehensive search of PubMed, and via the WHO COVID-19 research database of Embase and Medline databases, screening over 1,160 studies. While we cannot exclude that studies only available on other platforms may have been missed, this systematic review comprises over 30 million individuals from a total of 33 studies, thus providing a broad basis of evidence. In addition, each step of the study selection and quality assessment process was conducted independently by two researchers to limit the risks of selection and assessment bias.

Implications

The highly concurrent results and considerable patient counts do support a positive association between antibodies and reduced risk of SARS-CoV-2 infection. While the evidence is not quite as strong with regard to COVID-19 severity, high quality studies comprising high patient counts also support an association between higher antibody levels and better outcomes.

This suggests that defining antibody thresholds for efficient application of booster vaccinations would be useful for best protecting vulnerable patient groups, including older adults, obese or highly comorbid patient subsets. In addition, these cut-offs would be useful for early identification of high-risk patients at hospital admission and would allow for timely adjustment of therapy.

Thus far, several cut-offs have been suggested, most notably 250 BAU/mL for immunity [38] and 1,200 BAU/mL for protection against COVID-19 mortality [43]. However, additional data from separate cohorts is urgently needed to define and clarify protective thresholds for clinical use including advising susceptible patients on future booster vaccinations and identifying patients at high risk of adverse outcomes.

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References

1. World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard: situation by region, country, territory & area; 2023. https://covid19.who.int/table [Accessed 11 Dec 2023].
2. European Centre for Disease Prevention and Control. Data on testing for COVID-19 by week and country; 2023. https://www.ecdc.europa.eu/en/publications-data/covid-19-testing [Accessed 11 Dec 2023].
3. World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard. https://covid19.who.int/ [Accessed 11 Dec 2023].
4. Dyer O. Covid-19: infections climb globally as EG.5 variant gains ground. BMJ 2023;382:1900.
5. World Health Organization (WHO). Tracking SARS-COV-2-variants. https://www.who.int/activities/tracking-SARS-CoV-2-variants [Accessed 18 Jul 2023].
6. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
7. Steenblock C, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, et al. COVID-19 and metabolic disease: mechanisms and clinical management. Lancet Diabetes Endocrinol 2021;9:786–98.
8. Gasmi A, Peana M, Pivina L, Srinath S, Gasmi Benahmed A, Semenova Y, et al. Interrelations between COVID-19 and other disorders. Clin Immunol 2021;224:108651.
9. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet 2022;399:1303–12.
10. Centers for Disease Control and Prevention (CDC). Deaths by select demographic and geographic characteristics: provisional death counts for COVID-19. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm [Accessed 18 Jul 2023].
11. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against covid-19 in Israel. N Engl J Med 2021;385:1393–400.
12. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against covid-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385:2421–30.
13. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, et al. Protection by a fourth dose of BNT162b2 against omicron in Israel. N Engl J Med 2022;386:1712–20.
14. Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, et al. Association of a third dose of BNT162b2 vaccine with incidence of SARS-CoV-2 infection among health care workers in Israel. JAMA 2022;327:341–9.
15. Menni C, May A, Polidori L, Louca P, Wolf J, Capdevila J, et al. COVID-19 vaccine waning and effectiveness and side-effects of boosters: a prospective community study from the ZOE COVID study. Lancet Infect Dis 2022;22:1002–10.
16. Centers for Disease Control and Prevention (CDC). Interim clinical considerations for use of COVID-19 vaccines in the United States: summary of recent changes; 2023. (last updated May 12, 2023). https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html [Accessed 4 Sep 2023].
17. Du L, Yang Y, Zhang X. Neutralizing antibodies for the prevention and treatment of COVID-19. Cell Mol Immunol 2021;18:2293–306.
18. Seow J, Graham C, Merrick B, Acors S, Pickering S, Steel KJA, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat Microbiol 2020;5:1598–607.
19. Smoot K, Yang J, Tacker DH, Welch S, Khodaverdi M, Kimble W, et al. Persistence and protective potential of SARS-CoV-2 antibody levels after COVID-19 vaccination in a West Virginia nursing home cohort. JAMA Netw Open 2022;5:e2231334.
20. Gilboa M, Regev-Yochay G, Mandelboim M, Indenbaum V, Asraf K, Fluss R, et al. Durability of immune response after COVID-19 booster vaccination and association with COVID-19 omicron infection. JAMA Netw Open 2022;5:e2231778.
21. Grifoni A, Alonzi T, Alter G, Noonan DM, Landay AL, Albini A, et al. Impact of aging on immunity in the context of COVID-19, HIV, and tuberculosis. Front Immunol 2023;14:1146704.
22. Petráš M, Máčalík R, Janovská D, Čelko AM, Dáňová J, Selinger E, et al. Risk factors affecting COVID-19 vaccine effectiveness identified from 290 cross-country observational studies until February 2022: a meta-analysis and meta-regression. BMC Med 2022;20:461.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
24. WHO. WHO COVID-19 research database. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov [Accessed 1 Dec 2023].
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
26. Critical Appraisal Skills Programme. CASP cohort study checklist. 2018; 2018. https://casp-uk.net/images/checklist/documents/CASP-Cohort-Study-Checklist/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf [Accessed 6 Nov 2023].
27. Critical Appraisal Skills Programme. CASP case control study checklist. 2018; 2018. https://casp-uk.net/images/checklist/documents/CASP-Case-Control-Study-Checklist/CASP-Case-Control-Study-Checklist-2018-fillable-form.pdf [Accessed 6 Nov 2023].
28. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

29. Reynolds SL, Kaufman HW, Meyer WA, Bush C, Cohen O, Cronin K, et al. Risk of and duration of protection from SARS-CoV-2 reinfection assessed with real-world data. PLoS One 2023;18:e0280584.
30. Harvey RA, Rassen JA, Kabelac CA, Turenne W, Leonard S, Klesh R, et al. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 2021;181:672–9.
31. Fong Y, McDermott AB, Benkeser D, Roels S, Stieh DJ, an V, et al. Immune correlates analysis of the ENSEMBLE single Ad26.COV2.S dose vaccine efficacy clinical trial. Nat Microbiol 2022;7:1996–2010.
32. Hall VJ, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet 2021;397:1459–69.
33. Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science 2022;375:43–50.
34. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. N Engl J Med 2021;384:533–40.
35. Quiroga B, Soler MJ, Ortiz A, Jarava Mantecón CJ, Gomes Pérez VO, Bordils A, et al. Humoral response after the fourth dose of the SARS-CoV-2 vaccine in the CKD spectrum: a prespecified analysis of the SENCOVAC study. Nephrol Dial Transplant 2023;38:969–81.
36. Havervall S, Ng H, Jernbom Falk A, Greilert-Norin N, Månberg A, Marking U, et al. Robust humoral and cellular immune responses and low risk for reinfection at least 8 months following asymptomatic to mild COVID-19. J Intern Med 2022;291:72–80.
37. Jeffery-Smith A, Rowland TAJ, Patel M, Whitaker H, Iyanger N, Williams SV, et al. Reinfection with new variants of SARS-CoV-2 after natural infection: a prospective observational cohort in 13 care homes in England. Lancet Healthy Longevity 2021;2:e811–19.
38. Piñana JL, Vazquez L, Calabuig M, López-Corral L, Martin-Martin G, Villalon L, et al. One-year breakthrough SARS-CoV-2 infection and correlates of protection in fully vaccinated hematological patients. Blood Cancer J 2023;13:8.
39. Liu Z, Le K, Zhou X, Alexander JL, Lin S, Bewshea C, et al. Neutralising antibody potency against SARS-CoV-2 wild-type and omicron BA.1 and BA.4/5 variants in patients with inflammatory bowel disease treated with infliximab and vedolizumab after three doses of COVID-19 vaccine (CLARITY IBD): an analysis of a prospective multicentre cohort study. Lancet Gastroenterol Hepatol 2023;8:145–56.
40. Jeffery-Smith A, Iyanger N, Williams SV, Chow JY, Aiano F, Hoschler K, et al. Antibodies to SARS-CoV-2 protect against re-infection during outbreaks in care homes, September and October 2020. Euro Surveill 2021. https://doi.org/10.2807/1560-7917.ES.2021.26.5.2100092.
41. Wand O, Nacasch N, Fadeela A, Shashar M, Grupper A, Benchetrit S, et al. Humoral response and breakthrough infections with SARS-CoV-2 B.1.617.2 variant in vaccinated maintenance hemodialysis patients. J Nephrol 2022;35:1479–87.
42. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med 2021;27:2032–40.
43. Mink S, List W, Hoefle G, Frick M, Suessenbacher A, Winder T, et al. Evaluation of SARS-CoV-2 antibody levels on hospital admission as a correlate of protection against mortality. J Intern Med 2023;293:694–703.
44. Mink S, Saely CH, Leiherer A, Frick M, Plattner T, Drexel H, et al. Anti-SARS-CoV-2 antibody levels predict outcome in COVID-19 patients with type 2 diabetes: a prospective cohort study. Sci Rep 2023;13:18326.
45. Sananez I, Raiden SC, Algieri SC, Uranga M, Grisolía NA, Filippo D, et al. A poor and delayed anti-SARS-CoV2 IgG response is associated to severe COVID-19 in children. EBioMedicine 2021;72:103615.
46. Sanghavi DK, Bhakta S, Wadei HM, Bosch W, Cowart JB, Carter RE, et al. Low antispike antibody levels correlate with poor outcomes in COVID-19 breakthrough hospitalizations. J Intern Med 2022;292:127–35.
47. Sulaiman I, Chung M, Angel L, Tsay J-CJ, Wu BG, Yeung ST, et al. Microbial signatures in the lower airways of mechanically ventilated COVID-19 patients associated with poor clinical outcome. Nat Microbiol 2021;6:1245–58.
48. Yang H, Ma J, Li A, Lei J, Shang F, Cheng Y, et al. Inactivated vaccine injection and immunoglobulin G levels related to severe coronavirus disease 2019 (delta) pneumonia in Xi'an, China: a single-centered, retrospective, observational study. Front Cell Infect Microbiol 2022;12:933100.
49. Secchi M, Bazzigaluppi E, Brigatti C, Marzinotto I, Tresoldi C, Rovere-Querini P, et al. COVID-19 survival associates with the immunoglobulin response to the SARS-CoV-2 spike receptor binding domain. J Clin Invest 2020;130:6366–78.
50. Ruytinx P, Vandormael P, Fraussen J, Pieters Z, Thonissen S, Hellings N, et al. Comprehensive antibody and cytokine profiling in hospitalized COVID-19 patients in relation to clinical outcomes in a large Belgian cohort. Sci Rep 2023;13:19322.
51. Paggi R, Barbiero A, Manciulli T, Miftode A, Tilli M, Lagi F, et al. Characteristics of COVID-19 vaccinated and unvaccinated patients admitted to Careggi University Hospital, Florence, Italy. Intern Emerg Med 2023;18:821–30.
52. Bernal E, García-Villalba E, Pons E, Vicente MR, Tomás C, Minguela A, et al. Role of vaccination and anti-SARS-CoV-2 antibodies in the clinical outcome of hospitalized COVID-19 patients. Med Clin 2023;160:476–83.
53. Lucas C, Klein J, Sundaram ME, Liu F, Wong P, Silva J, et al. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat Med 2021;27:1178–86.
54. Klineova S, Farber RS, DeAngelis T, Leung T, Smith T, Blanck R, et al. Vaccine-breakthrough SARS-CoV-2 infections in people with multiple sclerosis and related conditions: an observational study by the New York COVID-19 Neuro-Immunology Consortium (NYCNIC-2). Mult Scler 2023;29:990–1000.
55. Dispinseri S, Secchi M, Pirillo MF, Tolazzi M, Borghi M, Brigatti C, et al. Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival. Nat Commun 2021;12:2670.
56. Al-Muhaiteeb A, AlSahow A, Al-Yousef A, AlHelal B, Alrajab H, Bahbahani Y, et al. Response to and outcomes of the Pfizer BNT162B2 vaccine in hemodialysis patients—a prospective observational study. Hemodial Int 2022;26:216–22.
57. Nagura-Ikeda M, Imai K, Kubota K, Noguchi S, Kitagawa Y, Matsuoka M, et al. Clinical characteristics and antibody response to SARS-CoV-2 spike 1 protein using VITROS Anti-SARS-CoV-2 antibody tests in COVID-19 patients in Japan. J Med Microbiol 2021. https://doi.org/10.1099/jmm.0.001291.
58. Yang HS, Racine-Brzostek SE, Karbaschi M, Yee J, Dillard A, Steel PAD, et al. Testing-on-a-probe biosensors reveal association of early SARS-CoV-2 total antibodies and surrogate neutralizing antibodies with mortality in COVID-19 patients. Biosens Bioelectron 2021;178:113008.
59. Malahe SRK, Hoek RAS, Dalm VASH, Broers AEC, den Hoed CM, Manintveld OC, et al. Clinical characteristics and outcomes of immunocompromised patients with coronavirus disease 2019 caused by the omicron variant: a prospective, observational study. Clin Infect Dis 2023;76:e172–8.

60. Shrivastava S, Palkar S, Shah J, Rane P, Lalwani S, Mishra AC, et al. Early and high SARS-CoV-2 neutralizing antibodies are associated with severity in COVID-19 patients from India. Am J Trop Med Hyg 2021;105: 401–6.
61. Lerum TV, Maltzahn NN, Aukrust P, Trøseid M, Henriksen KN, Kåsine T, et al. Persistent pulmonary pathology after COVID-19 is associated with high viral load, weak antibody response, and high levels of matrix metalloproteinase-9. Sci Rep 2021;11:23205.
62. Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. Eval Health Prof 2021;44:327–32.
63. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27:1205–11.
64. Suthar MS, Zimmerman MG, Kauffman RC, Mantus G, Linderman SL, Hudson WH, et al. Rapid generation of neutralizing antibody responses in COVID-19 patients. Cell Rep Med 2020;1:100040.
65. Sheward DJ, Kim C, Ehling RA, Pankow A, Castro Dopico X, Dyrdak R, et al. Neutralisation sensitivity of the SARS-CoV-2 omicron (B.1.1.529) variant: a cross-sectional study. Lancet Infect Dis 2022;22:813–20.
66. Larkin HD. Evolving omicron subvariants are more resistant to antibody therapy. JAMA 2022;328:518.
67. Henry C, Zheng N-Y, Huang M, Cabanov A, Rojas KT, Kaur K, et al. Influenza virus vaccination elicits poorly adapted B cell responses in elderly individuals. Cell Host Microbe 2019;25:357–66.e6.
68. Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130:1545–8.
69. Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5:eabe0367.
70. Qu J, Wu C, Li X, Zhang G, Jiang Z, Li X, et al. Profile of immunoglobulin G and IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:2255–8.
71. Milani GP, Dioni L, Favero C, Cantone L, Macchi C, Delbue S, et al. Serological follow-up of SARS-CoV-2 asymptomatic subjects. Sci Rep 2020;10:20048.
72. Rijkers G, Murk J-L, Wintermans B, van Looy B, van den Berge M, Veenemans J, et al. Differences in antibody kinetics and Functionality between severe and mild severe acute respiratory syndrome coronavirus 2 infections. J Infect Dis 2020;222:1265–9.
73. Drexel H, Rosano GMC, Lewis BS, Huber K, Vonbank A, Dopheide JF, et al. The age of randomized clinical trials: three important aspects of randomized clinical trials in cardiovascular pharmacotherapy with examples from lipid and diabetes trials. Eur Heart J Cardiovasc Pharmacother 2020;6:97–103.
74. Egger AE, Sahanic S, Gleiss A, Ratzinger F, Holzer B, Irsara C, et al. One-year follow-up of COVID-19 patients indicates substantial assay-dependent differences in the kinetics of SARS-CoV-2 antibodies. Microbiol Spectr 2022;10:e0059722.