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REVIEW ARTICLE

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Clinical predictors of SARS-CoV-2 neutralizing antibody titers in COVID-19 convalescents: Implications for convalescent plasma donor recruitment

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Abstract

While COVID-19 convalescent plasma (CCP) efficacy is still under investigation in randomized controlled trials (RCT), CCP collections continue worldwide with largely variable criteria. Since it is well known that only a minority of patients develop high-titer neutralizing antibodies (nAb), as assessed by the viral neutralization tests (VNT), strategies to maximize cost-effectiveness of CCP collection are urgently needed. A growing amount of the population is having exposure to the virus and is hence becoming a candidate CCP donor. Laboratory screening with high-throughput serology has good correlations with the VNT titer, but upstream screening using clinical surrogates would be advisable. We review here the existing literature on clinical predictors of high-titer nAb. Older age, male sex, and hospitalization are the main proxies of high VNT and should drive CCP donor recruitment.

KEYWORDS

clinical predictors, convalescent plasma, COVID-19, neutralizing antibodies, SARS-CoV-2, viral neutralization tests

1 | INTRODUCTION

The ongoing COVID-19 pandemic has caused more than 124 million cases and more than 2.5 million deaths worldwide as of March 2021. To date, there is only one drug whose efficacy has been unequivocally demonstrated in randomized controlled trials (RCT), namely dexamethasone. Many promising therapeutics have failed under RCTs, with COVID-19 convalescent plasma (CCP) having shown clinical benefit if used within 72 hours and with high neutralizing antibodies (nAb) titers;[1-6] on the contrary, trials lacking one of these requirements have failed to show clinical benefit.[1,7-9] Many more trials are still ongoing. CCP donations can be used in different ways,[10] and nAb titers, despite detectable at more than 8 months,[11] show a decline with time after recovery:[12] Hence CCP donor recruitment is being pursued to create bulk storages.

The cost for processing a CCP donation is considerably high due to personnel (donation nurses and laboratory technicians) and, in many regions, accessory testing (additional NAT, viral neutralization tests (VNT)), and pathogen reduction technologies. Additional concerns come from the risk of medical litigations in case of accidents during poorly selected CCP donations or prolonged storage of low-antibody units finally destined to discard.

While the pandemic accelerates, a growing number of eligible convalescents have to be screened as candidate CCP donor. While VNT remains the gold standard to proceed with donation, resource constraints have led to high-throughput serological surrogates,[12] which could similarly suffer bottlenecks or poor correlation. Given the need for cheap, simple, and efficient strategies to guide candidate donor recruitment in developing countries, we focused on clinical predictors of nAb titers, as measured by the VNT.

TABLE 1 Studies reporting correlation of nAb titer with clinical variables in COVID-19

Country (n)	Median nAb titer	Age (AOR)	Male sex (AOR)	Fever during acute illness (AOR)	Clinical severity by WHO ordinal scale (AOR)	Lymphocyte count	ABO blood group	Days since diagnosis	BMI	Ref
USA (250)	60% ≥1:80	1.03/year of age	2.08	2.73	6.59					34
USA (126)		0.1 every 10 y[a]	0.27[a]		0.86[a]			−0.192 every 10 d		41
USA (97)		No correlation	Trend	No correlation				No correlation		17
USA (221)				No correlation (fever vs. no fever)	Mean titer higher in ICU than in hospitalized higher than in HCW					26
USA (47)		Mean titer higher in age 48 to 75 y	No correlation							18
Austria (100)	1:230	$r^2 = .09$	Mean titer 1:60 in females vs. 120 in males		Mean titer 1:208 in WHO scores 1 and 2 vs.1:696 in WHO scores 3 and 4 (rank)					42
Brazil (149)							A/AB higher than B/O (rank)		>21 (rank)	33,43
China (175)	ID_{50} RLU	>40 y higher than <40 (ranks) $r = 0.4$				$r = -.44$				15
France (140)					x (ICU)					25
Germany (49)		No	x							24
Germany (62)		No	No		Duration and severity					44
Italy (494)	93% >1:80	0.26 (linear variable)	−0.14 (linear variable)		0.28 (linear variable)				No correlation	20
UK (330)	1:69	1.02 (linear variable)	2.41		2.25		AB/B higher than A/O (rank)	0.94 (linear variable)		16
Greece (60)		Age >50			Hospitalization			No correlation		45
China (23)					Mechanical ventilation higher than isolation wards					46
Spain (54)					No difference ICU vs non-ICU					47
USA (120)		Age >30	Yes		Yes				BMI >30	

Note: Abbreviations: AOR, adjusted odds ratio; nAb, neutralizing antibodies; BMI, body mass index; HCW, healthcare workers. x = AOR or correlation coefficient not reported. Empty cells mean the parameter was not investigated in that given study.

[a]Linear regression model coefficients.

2 | METHODS

A review of the literature about clinical predictors of PRNT in COVID-19 was done following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[13] PubMed (www.pubmed.gov), medrXiv (https://www.medrxiv.org), and biorXiv (https://www.biorxiv.org/) online databases were systematically searched. The search included articles from January 1, 2020 up to February 5, 2021. No restriction was placed on sample size. Only articles written in English were considered. The search query: "COVID19" AND "neutralizing" AND ("predictors" OR "proxies") was used for the first screening. The 293 search results were manually screened for consistency. The clinical parameters identified include age at diagnosis, days after initial diagnosis (positive nasopharyngeal swab), gender, hospitalization, and body mass index (BMI). Additionally, being largely available laboratory parameters, ABO blood group, and complete blood count were included as pseudo-clinical parameters.

3 | RESULTS

Table 1 summarizes the findings of 13 studies reporting the association of PRNT titer with clinical variables. Most studies agreed that higher age, male sex, higher BMI, and disease severity (especially hospitalization) are the main predictors for high PRNT titers. Other clinical factors such as fever during acute illness or days since diagnosis (or recovery) instead show correlations only in a minority of studies.[14] Single studies reported a low lymphocyte count[15] or AB/B blood groups as additional proxies:[16] These parameters, albeit not strictly clinical, are widely available for patients discharged from hospitals. One study found that GI symptoms did not predict nAb titer,[17] while another showed that abdominal pain, diarrhea, and low appetite correlated consistently with higher nAb levels.[14] A single study found no relation between nAb and symptom duration (1-7 vs 8-14 vs 15-28 days).[18] Similarly, a single study found no correlation between nAb and higher Charlson Comorbidity Index score.[14]

In the most relevant work to date, Mehew *et al* reported that, in a logistic regression model, younger age, female gender, blood group O, and not being a previous blood donor were associated with non-detectable neutralizing antibody response. The same authors used a multivariable gamma generalized linear model (GLM) to identify the factors associated with nAb titers: The analysis demonstrated a significant association between increasing mean nAb titers and increasing age, hospitalization (1:383 vs 1:63), male gender (1:97 vs 1:47), and B groups (1:148 for group AB vs 1:104 for group B, 1:70 for group A and 1:47 for group O).[16] Although it has been proposed that higher antibody levels in male and older patients simply relate to COVID-19 severity,[19] their model proposes that they remain associated with higher nAb titer levels after adjusting for hospitalization. In the largest study published so far by Del Fante and colleagues on 494 Italian CCP donors, the nAb titer was found to correlate positively with age and disease severity and negatively with female sex.[20]

4 | DISCUSSION

The VNT, while being a gold standard for nAb tittering, is a BSL3-requiring and time-consuming method whose high-throughput variants (eg, pseudotype VNT) are still to be implemented in the vast majority of laboratories. Scaling up of VNT for screening purposes is sustainable only when the recruitment is limited to interventional clinical trials. If the efficacy of CCP will be confirmed in RCT, at that point the number of convalescents to screen before CCP donation would be unsustainable for VNT, and likely an issue even for high-throughput serology (given the potential massive demand during a pandemic), if not filtered upstream with clinical proxies. We then started a review of clinical predictors of high nAb titers, as measured by the VNT.

This review has several limitations. Most studies we identified reported correlations but no cutoffs for clinical predictors. Additionally, the variability between VNT assays (titers, methods, live SARS-CoV-2 virus vs. pseudovirus, etc) is an additional hurdle for the derivation of cutoffs. Many studies were excluded from the analysis because they relied over high-throughput serology as a surrogate of nAb titer (eg,[21]).

Nevertheless, the 13 studies we analyzed support the feasibility of first-line screening with cost-free clinical surrogates such as age, sex, and hospitalization to identify the convalescents who are most likely to have high nAb titers as later measured by VNT. In resource-constrained settings, it is hence possible to orient the wave of CCP donations so that time and resource wasting is minimized. This study was limited to clinical proxies, but several studies identified additional, serological (eg, anti-Spike IgG avidity, $r = .4$,[22] or microfluidic affinity)[23] or non-serological biomarkers (eg, high C-reactive protein, $r = .5$)[15]: The utility of such specialistic laboratory biomarkers is reduced by their limited availability at the time of CCP donation screening, and, if unavailable, by their incremental cost, which largely overlap the one of high-throughput serology.

In most studies several patients (ranging from 2% in ICU to 25% in non-hospitalized patients[14,15,24,25] to 40% in healthcare workers)[26] show no nAb at all as assessed by the VNT. Lee *et al* reported that S-specific antibodies are capable of engaging dimeric FcγRIIa and FcγRIIIa decay linearly over time. S-specific antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADP) activity within plasma decline linearly as well, in line with the decay of S-specific IgG. Although there was significant decay in S-specific plasma ADCC and ADP activity, they remained readily detectable by all assays in 94% at 149 days, in contrast to nAbs, which were only detectable in 70%.[27] While this does not mean at all that the convalescents are not protected from further exposures (having immunity from specific T-lymphocytes),[28] this circumstance further increases the need for cost-effective screening strategies.

On average, the nAb titer peaks 30 days after symptom onset and declines by 25% every 15 days[17] (largely due to the decline in neutralizing IgM and IgA).[29,30] It is therefore sounding that the days since positive nasopharyngeal swab correlates with the nAb titer. Nevertheless there is large variability in decline kinetics. Grzelak

et al showed that the decline in nAbs was faster in males than in females, independently of age and BMI.[31] Titers ≥1:160 (which are considered the only useful donations for achieving clinical benefit) begin to decline significantly since day 60 (ie, 30 days after the peak).[32] Wendel *et al* reported that Ab titers ≥160 had a median persistence of 77 days after the onset of symptoms, but only 25% remained at this level after 100 days.[33] While decline around day 100 occurs in 90% of convalescents,[34] there was a high probability of sustaining nAb titers ≥160 when the initial nAb titer was ≥1280, weight ≥90kg, or BMI classified as overweight or obese. There was no correlation between ABO group, ABO isoagglutinin titers and persistent high nAb titers.[33] Of course, the initial nAb titer is only useful to evaluate the opportunity for repeated CCP donations.

Several SARS-CoV-2 variants are emerging,[35-37] and the efficacy of anti-Spike monoclonal antibodies against them seems lower than CCP.[38] Since even the currently marketed anti-Spike vaccines are likely to offer reduced protection against some of these variants,[39] the interest in CCP is likely to remain high for months. We anticipate that, with a growing population of convalescents, screening for CCP donation eligibility on the basis of clinical predictors will anticipate laboratory screening with both high-throughput serology and VNT, especially in resource-poor settings.

Additionally, collecting CCP from vaccinees is an intriguing opportunity, although to date the FDA is only allowing collection from vaccinees who have also been convalescents in the last 6 months.[40] Gaining knowledge about the breadth and duration of the immune response in COVID-19 vaccinees will likely contribute changing such regulations.

CONFLICT OF INTEREST

We declare we have no conflict of interests to disclose.

AUTHOR CONTRIBUTIONS

DF designed the paper, analyzed the data, and wrote the first draft. MF revised the final version.

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