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The kinetics of IgG Antibodies in Critically Ill Patients

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Abstract

the kinetics of SARS-CoV-2 antibodies response and factors predicting igG levels are still limited. We report a prospective analytical study of patients admitted for SARS-cov-2 in the medical intensive care unit of the Mohammed VI[th] University Hospital of Marrakech for three months.We measured the level of igG antibodies to SARS-Cov-2 on plasma blood samples from all patients collected on admission and then every seven days respectively until discharge or death. The kinetics of antibodies with disease progress were analyzed. The mean igG levels increased between ICU admission till day 21, then they dropped on day 28. Critical patients had higher igG levels than severe ones with no statistically significant difference. Between day one and day 14, males had higher igG levels than females; however, females had higher levels on days 21 and 28 with a statistically significant difference on day 28. On the chest CT scan, patients with ground-glass opacities and/or crazy paving distribution of 75% or more had higher igg levels with a statistically significant difference on day 7. In terms of mortality, deceased patients had higher igG levels with no statistically significant difference than survivors. Our results may suggest the incrimination of SARS-cov-2 igg antibody high level as a prognostic factor for disease severity.

Keywords: COVID-19 ; antibody ; illness severity ; immunoglobulin G ;SARS-CoV-2.

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1. Introduction

Coronavirus (2019-nCoV) was identified in 2019 in Wuhan, China. It causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) named COVID-19. It is a new coronavirus that has not yet been identified. Due to the rapid increase in cases, on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic [1].

Inter-human transmission of this virus occurs in two ways, directly through close contact with respiratory droplets generated by coughing and sneezing and indirectly by handling contaminated objects such as hands or others. After infection, The incubation period of COVID-19 ranges between 1 and 14 days, with the majority of cases manifesting within 3 to 5 days. The symptomatology consists in most cases of an influenza-like syndrome, fever, cough, and dyspnea. This infection often evolves towards the cure, but in some instances can be complicated and gives off severe forms, hypoxemic pneumonia, a syndrome of acute respiratory distress, or acute lesional lung edema that requires mechanical ventilation in the intensive care unit [2,3].

This virus is composed of an envelope surrounding a helicoidal capsid, which contains the genetic material in which we have a single-stranded RNA. The viral envelope comprises phospholipids, making this virus very fragile in the external environment and permeable to water and alcohol [4,5].

The immune system responds to SARS-CoV-2 infection by producing specific antibodies that reflect the primary humoral immune response to defend against foreign agents. These antibodies appear in a few days to two weeks. The IgM isotype appears from day 7, and the IgG from day 10 on average[6-10].

The detection of these antibodies indicates exposure to the 2019-nCoV, but several questions remain unanswered. It is not yet known whether the presence of antibodies confers protection (neutralizing antibodies), nor whether this protection persists over time [11,12]. Previous studies have shown that the level of IgG antibodies was influenced by disease severity, comorbidities, and immunosuppression. Besides, the IgG response can persist for up to 8 months after the onset of symptoms, but data on factors predicting IgG levels are still limited [11].

Our purpose was to study the kinetics of IgG antibodies in critically ill patients.

2. Materials and Methods

2.1. Patients

This study was a prospective analytical study of patients admitted for SARS-CoV-2 in the medical intensive care unit of the Mohammed VIth University Hospital of Marrakech for three months (from November 2020 to January 2021). Patients over 18 years with SARS-CoV-2 confirmed by real-time quantitative Polymerase Chain Reaction (RT-qPCR).
We measured the level of IgG antibodies to SARS-Cov-2 on plasma blood samples from all patients collected on admission (day 1) and then every seven days respectively until discharge or death. We considered the first

day of symptoms onset as the start of the COVID-19 infection.

2.2. Biological principles of the procedure [13]

The SARS-CoV-2 IgG assay is designed to detect class G (IgG) antibodies to the core protein of SARS-CoV-2. We used the SARS-CoV-2 IgG 6R86 Reagent Kit in this study. The test is an automated two-step immunoassay for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma using chemiluminescent microparticle immunoassay technology (CMIA).

The sample, paramagnetic SARS-CoV-2 antigen-coated microparticles and test diluent are combined and incubated. Anti-SARS-CoV-2 IgG antibodies in the sample bind to the SARS-CoV-2 antigen-coated microparticles. The mixture is washed. The acridinium-labelled products labeled products are added to create a reaction mixture and incubated with an anti-human IgG conjugate. After a wash cycle, the pre-trigger and trigger solutions are added. The resulting chemiluminescent response is measured as a relative light unit (RLU).

The presence/absence of IgG antibodies is determined by comparing the chemiluminescent RLU in response to the calibrator RLU, calculated as an index (S/C)

2.3. Interpretation of Results

The ARCHITECT i-System calculates the average signal of the chemiluminescent calibrator fromt hree replicas of the calibrator and stores the result. Results are reported by dividing the sample result by the stored calibrator result. The default result unit for the SARS-CoV-2 IgG test is the index (S/C). The cut-off value for a positive SARS-CoV-2 test result has been set at

1.4. signal/threshold units (S/CO)[13]

2.4. Ethics

We have obtained written informed consent from patients and respected their anonymity.

2.5. Statistical analysis

All statistical analysis was performed using SPSS software (version 10.0; SPSS, Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corporation, Washington, USA). Statistical comparisons were performed using the chi-square test. A probability (p) value less than 0.05 was considered statistically significant.

Conflict of interest

The authors declare no conflict of interest.

3. Results

From November 2020 to January 2021, 60 patients with at least one positive polymerase chain reaction (PCR) were tested for IgG. The mean age was 60 ± 14.5 years, with a predominance of the male gender (75%). Diabetes mellitus was the most frequent underlying disease (25%). Non-invasive and invasive ventilation was required in 57.6 % and 13.6%, respectively. The ICU mortality rate was 39% of cases (Table 1).

Table 1: Baseline characteristics of the 60 patients.

Variables		**Statistics**
Age (year), mean ± SD		60±14.5
Gender, n (%)	Male	45 (75)
	Female	15 (25)
Comorbidities, n (%)	Yes	35 (58)
	Diabetes mellitus	15 (25)
	Hypertension	12 (20)
	Cardiopathy	3 (5)
	Solid tumor	2 (3.3)
	Chronic obstructive pulmonary disease	1 (1.7)
	Hematological disease	1 (1.7)
	Connective tissue disease	1 (1.7)
The time between first symptom and ICU admission (day), mean ± SD		12±5
Glasgow coma scale at ICU admission, mean ± SD		15±2
Pulsed oxygen saturation at ICU admission, mean ± SD		90±8
PaO_2/FiO_2 at ICU admission, median (IQR)		120 (75-200)
Lymphocytes at ICU admission (/mm^3), median (IQR)		720 (570-1100)
Ferritinemia at ICU admission (ng/mL), median (IQR)		986 (470-1900)
Immunoglobulin G at admission (index value), median (IQR)		5.5 (1-8)
Immunoglobulin G at day 7 (index value), median (IQR)		6 (4-8)
Immunoglobulin G at day 14 (index value), median (IQR)		6 (4.5-7)
Immunoglobulin G at day 21 (index value), median (IQR)		7 (5-8)
Immunoglobulin G at day 28 (index value), median (IQR)		6.5 (4-8)
CT scan, ground-glass opacity and/or crazy paving distribution, n (%)	Performed	54 (90)
	<25 %	11 (20.4)
	25-49 %	15 (27.8)
	50-75 %	18 (33.3)
	>75 %	10 (18.5)
Need of non-invasive ventilation, n (%)		34 (57.6)
Need of invasive ventilation, n (%)		8 (13.6)
Anticoagulation, n (%)		60 (100)
Need of noradrenaline, n (%)		4 (6.8)
ICU length of stay (day), median (IQR)		9 (6-17)
Mortality, n (%)		23 (39)

The mean IgG levels increased between ICU admission till day 21, then they dropped on day 28 (Figure 1). Critical patients had higher IgG levels than severe ones with no statistically significant difference (Figure 2-A). Between day one and day 14, males had higher IgG levels than females; however, females had higher levels on days 21 and 28 with a statistically significant difference on day 28 (p=0.02) (Figure 2-B). On the chest CT scan, patients with ground-glass opacities and/or crazy paving distribution of 75% or more had higher IgG levels with a statistically significant difference on day 7 (Figure 2-C). In terms of mortality, deceased patients had higher IgG levels with no statistically significant difference than survivors (Figure 2-D).

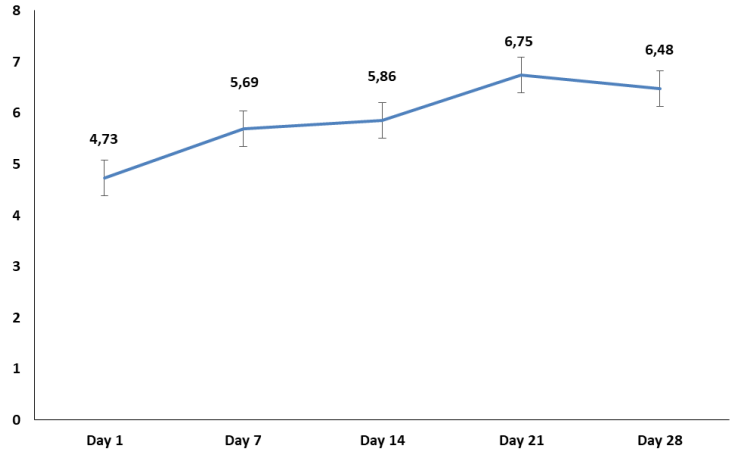

Figure 1: Kinetic of lgG levels since the ICU admission of all patients

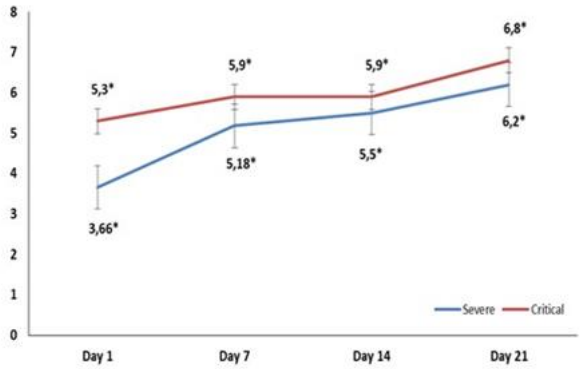

Figure 2-A: Kinetics of lgG levels in severe and critical patients since the ICU admission. *p>0.05

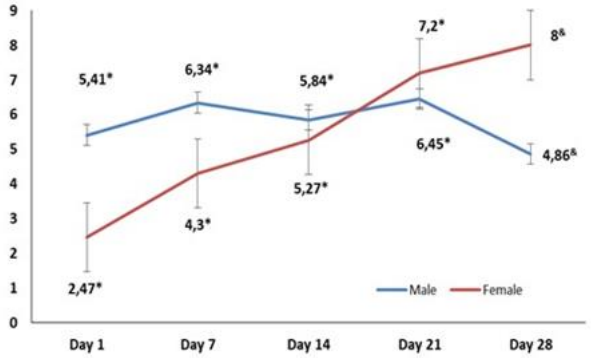

Figure 2-B: Kinetics of lgG levels in female and male patients since the ICU admission. *p>0.05; &: p=0.02

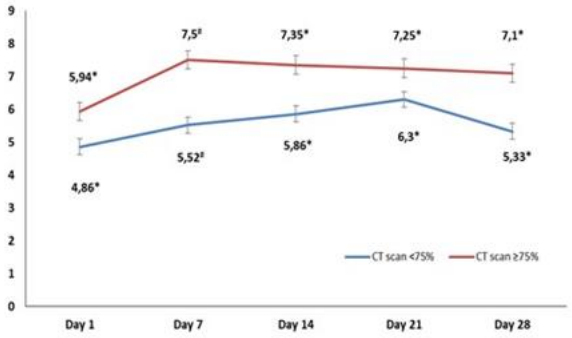

Figure 2-C: Kinetics of lgG levels since the ICU admission in patients according to the CT scan lesions distrbution. *p>0.05; #: p=0.01

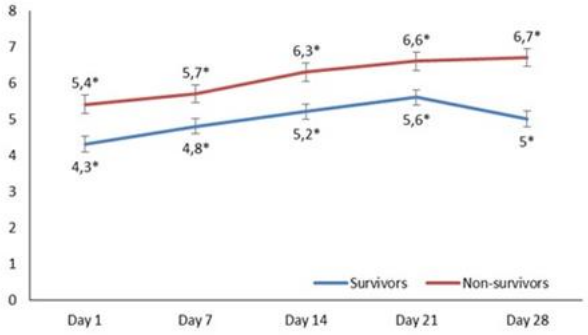

Figure 2-D: Kinetics of lgG levels in survivors and non-survivors patients since the ICU admission. *p>0.05

4. Discussion

Since we are dealing with a newly emerged virus, understanding the kinetics of SARS-CoV-2 antibodies is essential for early detection and intervention in potentially severe patients. Despite several studies, the humoral immune response of patients with COVID-19 remains largely unknown. During SARS-CoV-2 infection, specific antibodies against the virus are produced in most patients except those with severe immunosuppression [14]. IgM antibodies, the first line of defense, can be detected as early as three days after infection, while IgG antibodies are detected later (on average 14 days after the onset of disease) and may persist for several months after infection and serve as an indicator of the previous condition [7-11]. Still, the duration of their persistence remains unknown.

Our patients were aged 60±14 years, of which 75 % were male. Several authors have studied factors aggravating the disease due to COVID 19; age and sex seem to be essential elements to consider. Indeed, elderly subjects (60-85 years) had significantly higher neutralizing antibody titers than younger patients [15,16]. This male predominance can be explained by the higher prevalence of chronic disease in males compared and the sex hormones that may, in some cases, contribute to the worsening of clinical symptoms [17,18]. Of all included, 36% of critically ill patients had died. This mortality rate was related to comorbidities, lung involvement, biological disturbance, and delayed care (Table 1).

In our patients, the level of IgG antibodies increased progressively until the 21st day after the

beginning of the infection, then decreased progressively from the 28th day. The Antibody titer up to three weeks after the start of the disease (figure 2A). Previous studies have reported controversial results, with some publications describing a significant relationship between disease severity and antibody levels [14,19,20,21]. However, others did not, with only ten patients with severe symptomatology [22]. In our study we didn't detect a significant correlation between the severity of symtomatology and the level of antibodies, but this may be due to our small sample size.

SARS-CoV-2 infection triggered the humoral and cellular immune response. However, uncontrolled inflammatory humoral responses and impaired cellular immune responses can lead to severe tissue damage [23].

It remains unclear whether the SARS-CoV-2 antibody response results in virus neutralization

or contributes to pathogenicity in severe disease COVID-19 [23]. Antibody levels appear to be

related to host protection and viral neutralization, but in rare cases, antibodies may constitute

a hazard by promoting disease progression, resulting in a phenomenon known as antibody-

dependent enhancement (ADE) [24,25]. In the case of SARS-CoV-2, ADE has promoted uptake of the virus by macrophages, resulting in elevated production of inflammatory cytokines [23]. This phenomenon also inhibits the control of inflammation, especially in the lungs, kidneys, and others, leading to organ failure, explaining the acute respiratory distress syndrome and other inflammatory organ damage seen in severe COVID-19 patients [25-27].

5. Conclusion

Although the relationship between disease and humoral response is not well-illustrated.Our results may suggest the incrimination of SARS-CoV-2 IgG antibody high level as a prognostic factor for disease severity.

6. Research Limitations

The lack of information on the date of covid PCR positivity for patients transferred from other institutions; and the number of our samples was not very large because the number of intensive care unit places was limited.

References

[1] Coronavirus Disease (COVID-19) Situation Reports n.d. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed November 23, 2021).

[2] Maladie à coronavirus (COVID-19) | UNICEF n.d. https://www.unicef.org/morocco/recits/maladie-

%C3%A0-coronavirus-covid-19 (accessed November 23, 2021).

[3] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929–36. https://doi.org/10.1056/NEJMoa2001191.

[4] Tyrrell DAJ, Myint SH. Coronaviruses. In: Baron S, editor. Medical Microbiology. 4th ed., Galveston (TX): University of Texas Medical Branch at Galveston; 1996.

[5] van Dorp L, Acman M, Richard D, Shaw LP, Ford CE, Ormond L, et al. Emergence of genomic diversity and recurrent mutations in SARS-CoV-2. Infection, Genetics and Evolution 2020;83:104351. https://doi.org/10.1016/j.meegid.2020.104351.

[6] Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clinical Infectious Diseases 2020;71:778–85. https://doi.org/10.1093/cid/ciaa310.

[7] Long Q-X, Liu B-Z, Deng H-J, Wu G-C, Deng K, Chen Y-K, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26:845–8. https://doi.org/10.1038/s41591-020-0897-1.

[8] Li G, Chen X, Xu A. Profile of Specific Antibodies to the SARS-Associated Coronavirus. New England Journal of Medicine 2003;349:508–9. https://doi.org/10.1056/NEJM200307313490520.

[9] Covid-19 : bientôt des tests pour vérifier l'efficacité de votre vaccin ? n.d. https://www.futura-sciences.com/sante/actualites/coronavirus-covid-19-bientot-tests-verifier-efficacite-votre-vaccin-86884/ (accessed November 23, 2021).

[10] Xiao AT, Gao C, Zhang S. Profile of specific antibodies to SARS-CoV-2: The first report. Journal of Infection 2020;81:147–78. https://doi.org/10.1016/j.jinf.2020.03.012.

[11] Sun B, Feng Y, Mo X, Zheng P, Wang Q, Li P, et al. Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients. Emerging Microbes & Infections 2020;9:940–8. https://doi.org/10.1080/22221751.2020.1762515.

[12] Wang X, Guo X, Xin Q, Pan Y, Hu Y, Li J, et al. Neutralizing Antibody Responses to Severe Acute Respiratory Syndrome Coronavirus 2 in Coronavirus Disease 2019 Inpatients and Convalescent Patients. Clinical Infectious Diseases 2020;71:2688–94. https://doi.org/10.1093/cid/ciaa721.

[13] download.pdf n.d.

[14] Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clin Infect Dis 2020;71:2027–34. https://doi.org/10.1093/cid/ciaa344.

[15] Hotez PJ, Corry DB, Bottazzi ME. COVID-19 vaccine design: the Janus face of immune enhancement. Nat Rev Immunol 2020;20:347–8. https://doi.org/10.1038/s41577-020-0323-4.

[16] Perera RA, Mok CK, Tsang OT, Lv H, Ko RL, Wu NC, et al. Serological assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), March 2020. Eurosurveillance 2020;25:2000421. https://doi.org/10.2807/1560-7917.ES.2020.25.16.2000421.

[17] Wolfe J, Safdar B, Madsen TE, Sethuraman KN, Becker B, Greenberg MR, et al. sex- or Gender-specific Differences in the Clinical Presentation, Outcome, and Treatment of SARS-CoV-2. Clinical Therapeutics 2021;43:557-571.e1. https://doi.org/10.1016/j.clinthera.2021.01.015.

[18] Majdoub Fehri S, Abdelmouleh K, Ghorbel H, Khrouf M, Fezai N, Kwas H. Infection COVID-19 selon le sexe : quelle relation ? Revue des Maladies Respiratoires Actualités 2021;13:113–4. https://doi.org/10.1016/j.rmra.2020.11.235.

[19] Ko J-H, Joo E-J, Park S-J, Baek JY, Kim WD, Jee J, et al. Neutralizing Antibody Production in Asymptomatic and Mild COVID-19 Patients, in Comparison with Pneumonic COVID-19 Patients. Journal of Clinical Medicine 2020;9. https://doi.org/10.3390/jcm9072268.

[20] Zhang X, Lu S, Li H, Wang Y, Lu Z, Liu Z, et al. Viral and Antibody Kinetics of COVID-19 Patients with Different Disease Severities in Acute and Convalescent Phases: A 6-Month Follow-Up Study. Virol Sin 2020;35:820–9. https://doi.org/10.1007/s12250-020-00329-9.

[21] Bai Z, Li Q, Chen Q, Niu C, Wei Y, Huang H, et al. Clinical significance of serum IgM and IgG levels in COVID-19 patients in Hubei Province, China. Journal of Intensive Medicine 2021:S2667100X21000311. https://doi.org/10.1016/j.jointm.2021.09.001.

[22] To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases 2020;20:565–74. https://doi.org/10.1016/S1473-3099(20)30196-1.

[23] Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 2020;20:269–70. https://doi.org/10.1038/s41577-020-0308-3.

[24] Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol 2020;20:339–41. https://doi.org/10.1038/s41577-020-0321-6.

[25] Is COVID-19 receiving ADE from other coronaviruses? | Elsevier Enhanced Reader n.d. https://doi.org/10.1016/j.micinf.2020.02.006.

[26] Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK. Severe Acute Respiratory Syndrome (SARS)

Coronavirus-Induced Lung Epithelial Cytokines Exacerbate SARS Pathogenesis by Modulating Intrinsic Functions of Monocyte-Derived Macrophages and Dendritic Cells. Journal of Virology 2009;83:3039–48. https://doi.org/10.1128/JVI.01792-08.

[27] Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. Cell Host Microbe 2016;19:181–93. https://doi.org/10.1016/j.chom.2016.01.007.