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Title: Rapid diagnosis of SARS-CoV-2 infection by detecting IgG and IgM antibodies with an immunochromatographic device: a prospective single-center study

Running title: Rapid serologic test to diagnose SARS-CoV-2 infection

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Abstract

Objectives:

SARS-CoV-2 infection constitutes a diagnostic challenge in patients from 2-3 weeks after the onset of symptoms, due to the low positivity rate of the PCR, especially in upper respiratory samples. Serologic tests based on ELISA have been developed and evaluated as useful complements to PCR in these situations. However, there is scarce information about the usefulness of rapid tests based on immunochromatography. The aim of our study was to analyze the diagnostic performance of these rapid tests in COVID-19 pneumonia patients.

Methods:

We evaluated an immunochromatographic test (*AllTest COV-19 IgG / IgM kit*) which detects IgG and IgM antibodies. First, we performed a validation of the serologic test using serum samples from 45 healthy control patients (group 1) and 55 confirmed by PCR cases of COVID-19 (group 2) in order to establish the specificity and sensitivity, respectively. Then we prospectively employed the test in 63 patients diagnosed with pneumonia of unknown etiology that were SARS-CoV-2 negative by PCR (group 3), to establish the diagnostic performance in these patients.

Results:

All patients from group 1 (healthy controls) resulted negative for the serologic test (specificity = 100%). Regarding group 2 (PCR positive) patients, the median time from the onset of symptoms was 11 days and the test was positive for either IgM or IgG in 26 out of 55 patients (overall sensitivity = 47.3%). However, in those patients with 14 days or more from onset of symptoms, the sensitivity was 73.9%. Regarding group 3 patients, the median days from onset of symptoms was 17 and the test was positive in 56 out of 63 patients (88.9% positivity rate). In these group 3 patients with 14 days or more from onset of symptoms, the positivity rate was 91.1%.

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Conclusions:

Our study shows that serologic rapid tests can be used as a complement of PCR to diagnose SARS-CoV-2 infection after 14 days from the onset of symptoms. These immunochromatographic devices could be especially useful in hospitalized patients with pneumonia of unknown etiology with 14 or more days from the onset of symptoms and in whom the PCR has been negative.

Keywords:

SARS-CoV-2; COVID-19; serology; inmunocromatography; rapid test

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Introduction

The pandemic due to SARS-CoV-2 that started in Wuhan four months ago (1,2) has caused until April 8th a total of 1,353,361 cases and 79,235 deaths worldwide (3). Spain is the country of the European region that has been most affected by the infection, accounting for 140,510 cases and 13,798 deaths by April 8th (3). From the beginning of the pandemic, one of the main concerns to deal with was the complexity and excessive time to results of the diagnostic test, based on polymerase chain reaction (PCR). Few clinical microbiology laboratories were prepared at this time to process such a massive volume of samples that grew exponentially. In our hospital, which is a middle sized center (440 beds), from March 5th to April 6th, a total of 7,453 respiratory samples (the vast majority nasopharyngeal exudates) were processed for SARS-CoV-2 PCR, reaching a positivity rate between 20 and 40%. Another added problem was the low positivity rate of nasopharyngeal samples in patients presenting a clinical syndrome compatible with COVID-19 in the second and third week of infection (1,4), which is generally the period in which patients get worse and are admitted to the hospital (1). On the other hand, most patients present a non-productive cough (5); this fact, together with the high risk of generating aerosols in bronchoscopies explains that most respiratory samples came from the upper respiratory tract, where the virus concentration is lower beyond the first week after the onset of symptoms (6,7). As a consequence, the positivity rate of the PCR in these patients could be lower than expected and many of them were hospitalized with a provisional diagnosis of pneumonia of unknown etiology and possible COVID-19.

In order to overcome these limitations, different microplate ELISA tests have been developed. Recently published studies confirm the usefulness of combining PCR in nasopharyngeal exudates and the detection of IgM and IgG antibodies in the blood of patients (8). The combination of both molecular and serologic techniques allowed some authors to achieve a sensitivity of 97% for diagnosis of SARS-CoV-2 infection (9). However, these tests based on ELISA are not as suitable for clinical use as rapid tests because they are time-consuming and, as a matter of fact, cannot be included in the management algorithms in emergency departments (8,9).

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Since the beginning of the epidemic in Spain, we received information about the availability of rapid serological diagnostic kits that detected IgG and IgM antibodies using immunochromatographic (ICT) devices. However, there are very few published studies about the clinical application of these kits (10). The aim of our study was to evaluate the diagnostic performance of one of these serologic rapid tests, first by a validation of the test in healthy patients and confirmed cases of COVID-19 and then by a prospective evaluation in patients with pneumonia of unknown etiology and a clinical diagnosis of COVID-19 with negative PCR for SARS-CoV-2.

Methods

Population and study period:

We included 3 groups of patients in our study:

Group 1 (healthy controls): randomly selected patients who had a serum sample taken for other serology studies, from October 1 to November 30, 2019 (before the first cases of COVID-19 were reported).

Group 2 (confirmed cases of SARS-CoV-2 infection): patients that were admitted to the Emergency department between March 1 and April 6, 2020, with suspicion of COVID-19. The PCR was positive for SARS-CoV-2 for all of them.

Group 3 (pneumonia of unknown etiology): patients who had been admitted for at least 5 days between February 9 and April 2, 2020, with a clinical and radiological diagnosis of pneumonia of unknown etiology, in which the PCR for SARS-CoV-2 was negative. They were prospective studied after the validation of the serologic test.

Diagnostic methods:

Molecular techniques: Two automatic extractors were used to obtain viral RNA from clinical samples: *MagCore HF16* (RBC bioscience, Taipei, Taiwan) and *Hamilton Microlab Starlet* (Hamilton Company, Bonaduz, Switzerland). RNA amplification was made using two real-time PCR platforms: *VIASURE SARS-*

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CoV-2 Real Time PCR Detection Kit (Certest Biotech, Zaragoza, Spain) and *Allplex 2019-nCoV assay* (Seegene, Seoul, South Korea). These kits were used according to the manufacturer's instructions for both the handling and the interpretation of the results.

Serology: we applied the *AllTest COV-19 IgG / IgM kit* (AllTest Biotech, Hangzhou, China) for the serological diagnosis. This test is a qualitative membrane-based immunoassay (immunochromatography) for the detection of IgG and IgM antibodies against SARS-CoV-2 in whole blood, serum or plasma samples. We used 10µL of serum for the performance of the test. For the healthy control group (group 1), cryopreserved archive samples were obtained, which were previously defrosted and tempered to room temperature before analysis. The performance of the test and the interpretation of the results were done according to the manufacturer's instructions.

Clinical data:

Demographic and clinical variables of the study population were obtained from the medical records. The clinical variable of time from the onset of symptoms was calculated in groups 2 and 3 from the day of onset of symptoms to the day of the extraction of the sample of serum.

Serologic test validation:

The serologic test was evaluated on clinical samples from group 1 and 2 in order to assess the sensitivity and specificity of the test:

Group 1 (healthy controls): they were used to evaluate the specificity (Sp) of the serological test. 45 aliquots of cryopreserved sera, corresponding to 45 different controls, were recovered from the serum archive.

Group 2: (patients SARS-CoV-2 positive by PCR): they were used to evaluate the sensitivity (Sn) of the serological test, using PCR as a gold standard. A total of 55 confirmed cases of SARS-CoV-2 infection were included, and cryopreserved aliquots of serum of those patients were used. Those aliquots were previously obtained from samples sent to the laboratory to carry out other serologic tests.

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Diagnostic performance of the serologic test:

The assessment was performed on patients from group 3 (pneumonia of unknown etiology with negative PCR for SARS-CoV-2). Serum samples from 63 patients were studied. These samples were obtained from fresh patient serum samples sent for other determinations to the laboratory the same day the analysis was performed.

Statistical analysis:

Sensitivity was evaluated in group 2, using the PCR as a gold standard, and specificity was evaluated with group 1 patients. For the evaluation of diagnostic performance, we evaluated the number of patients belonging to group 3 that were diagnosed with SARS-CoV-2 infection with the serologic test. We considered a positive result for samples in which IgG, IgM or both of them were detected. Continuous variables are expressed as median and interquartile range (IQR) and categorical variables as proportions. Comparisons between categorical variables were made using the Chi-squared or Fisher's exact two-tailed test and the Mantel-Haenszel test for linear trends. For these comparisons, a *p* value less than or equal to 0.05 was considered significant. Statistical analysis was performed with SPSS v20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 163 patients were studied [62 (51-74) years; 107 (65.6%) male]. The serologic results from the three groups of patients are summarized in Table 1.

Considering all patients included in groups 2 and 3 (n=118), we found an increase of IgG and IgM detection after seven days from onset of symptoms (p=0,048 for IgM and p≤0,001 for IgG).

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Table 1. Serologic results from the three groups of patients.

Group of patients	**Group 1**	**Group 2**	**Group 3**	
No. patients	45	55	63	
Age (years)	55 (34-66)	63 (50-79)	67 (57-74)	
Sex (male)	27(60,0%)	33 (60,0%)	47(74%)	
Time from onset of symptoms (days)	Not applicable	11 (7-23)	17 (13-22)	
IgG positive	0 (0%)	23 (41.8%)	56 (88.9%)	
IgM positive	0 (0%)	12 (21.8%)	25 (39.7%)	
Positive result	0 (0%)	26 (47.3%)	56 (88.9%)	
Serologic results of group 2 patients, depending on the time from the onset of symptoms				
Time from onset of symptoms	**< 7 days**	**7-13 days**	**≥ 14 days**	***p*-value**
No. patients	8 (14.5%)	24 (43.6%)	23 (41.8%)	-
IgG positive	1 (12.5%)	6 (25.0%)	16 (69.6%)	**≤0.001**
IgM positive	0 (0%)	3 (12.5%)	9 (39.1%)	**0.008**
Positive result	1 (12.5%)	8 (33.3%)	17 (73.9%)	**≤0.001**
Serologic results of group 3 patients, depending on the time from the onset of symptoms				
Time from onset of symptoms	**<7 days**	**7-13 days**	**≥ 14 days**	***p*-value**
No. patients	0 (0%)	18 (28.6%)	45 (71.4%)	-
IgG positive	0 (0%)	15 (83.3%)	41 (91.1%)	0.379
IgM positive	0 (0%)	7 (38.9%)	18 (40.0%)	0.936
Positive result	0 (0%)	15 (83.3%)	41 (91.1%)	0.379

Group 1 (healthy controls); Group 2 (PCR positive); Group 3 (pneumonia of unknown etiology and negative PCR). IQR: interquartile range; PCR: polymerase chain reaction.

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Serologic test validation:

All patients included in the group 1 showed negative results for serological tests. Thus, the serological test presented a specificity of 100%. The overall sensitivity of the test was 47.3% compared to PCR (Table 1). An increase in sensitivity was found after seven days from onset of symptoms ($p=0.033$), and as the days with symptoms progressed ($p\leq0.001$) (Figure 1). However a reduction was detected in the fourth week (53.8%) compared to third week (83.3%), not being statistically significant ($p=0.333$). After the fourth week, the positivity rate for IgG antibodies increased, thus reaching a positivity rate of 100%.

Diagnostic performance of the serologic test:

We assessed the serologic test in the group 3 patients. Antibodies against SARS-CoV-2 were detected in 56 out of 63 patients (88.9%), being 100% of them positive for IgG antibodies, and 39.7% positive also for IgM antibodies (Table 1). No patient had less than 7 days from onset of symptoms. The positivity rate increased from 7-13 days (83.3%) to ≥14 days (91.1%), but there were no statistically significant differences between weeks ($p=0.087$) (Table 1 & Figure 1). In a similar way as group 2 patients, we observed a slight decrease in the positivity rate in the fourth week after onset of symptoms for IgG antibodies (73.3%) ($p=0.260$), and after the fourth week, the positivity rate for IgG antibodies increased, thus reaching a positivity rate of 100% (Figure 1).

Figure 1. Temporal evolution of the percentage of positivity for the different antibodies considering: a) Group 2 and group 3, b) only group 2, and c) only group 3.

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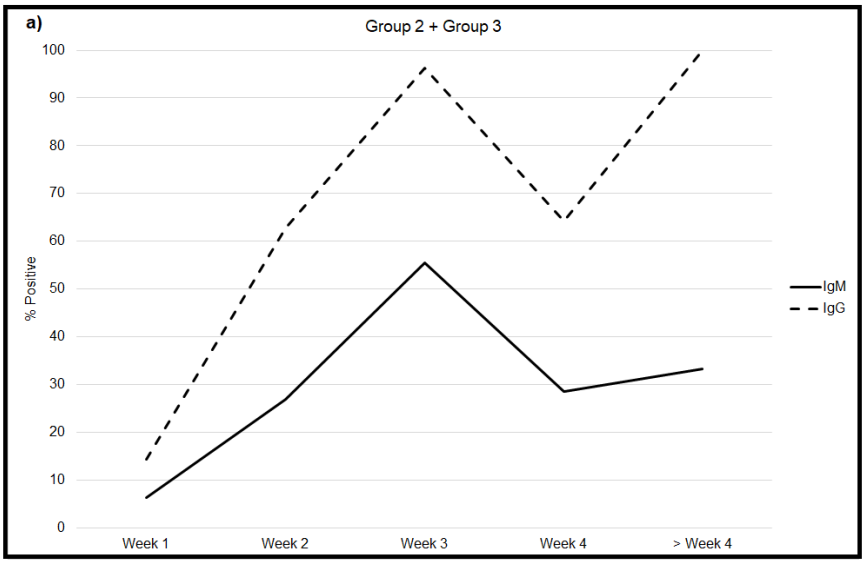

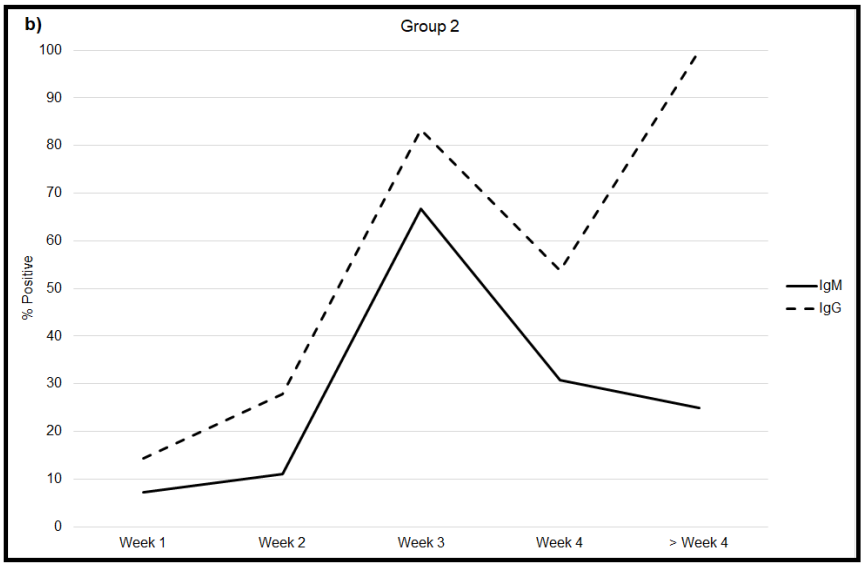

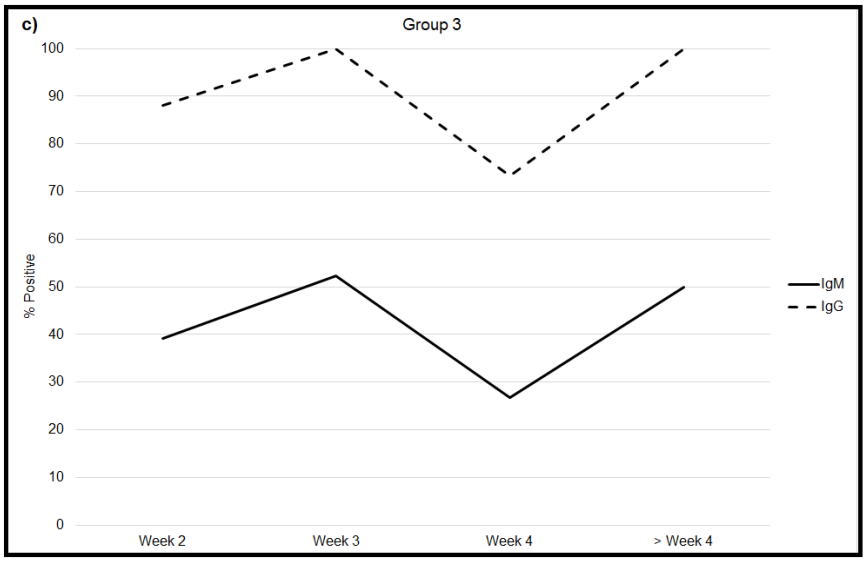

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Discussion

Our study shows that immunochromatographic tests are reliable to diagnose SARS-CoV-2 infection from 14 days of onset of symptoms. Serologic rapid tests could be especially useful diagnostic tools in hospitalized patients with pneumonia of unknown etiology with 14 or more days from the onset of symptoms and in whom the PCR has been negative.

The current situation of the COVID pandemic requires an urgent and coordinated answer to the inherent problems of the PCR-based diagnosis: on the one hand the low capacity to carry out the PCR techniques in some laboratories and also the low sensitivity of the PCR test in nasopharyngeal samples, specially from the second week of infection (2,4). This study shows that the rapid test for the detection of IgG and IgM Alltest® is very specific (100%) and reaches a sensitivity of 73.9% from day 14 of onset of symptoms in patients with previous positive PCR in a nasopharyngeal exudate. There is increasing evidence on the usefulness of serology for diagnosis of SARS-CoV-2 infection, but most of these studies are based on microplate ELISA tests to detect IgA, IgM and IgG antibodies (8,9). These techniques have shown high sensitivity and specificity but they also require special equipment, trained personnel and take several hours to perform. Due to this, there is an increasing interest about the usefulness of serologic rapid tests, but there is scarce information about their diagnostic performance. In a recently published study, Liu et als. (6) performed a multicenter evaluation of a serologic rapid test that the authors had developed. In their study, the overall sensitivity was 88.7% and the specificity was 90.6%. However, although they achieved a higher sensitivity than that obtained in our study, these authors did not present data about the time after the onset of symptoms except from 58 out of 525 patients enrolled in the study. Besides, for this subgroup of patients they only described that the time from the onset of symptoms was 8 to 33 days. Maybe there was a selection bias in the enrolled patients and most of the recruited cases had long evolution times, which would justify these results in sensitivity. To the best of our knowledge, our study is the first evaluation of this serologic rapid test which has complete data on the time from the onset of symptoms. As this is a serological test, this kind of information is key in order to interpret properly the sensitivity and specificity results.

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Additionally, in our experience, the use of these tests allowed retrospective diagnosis of COVID-19 infection in 91.1% of a group of 63 patients admitted with a clinical diagnosis of COVID-19 pneumonia and negative PCR in nasopharyngeal exudate. According to our data, the vast majority of patients seroconvert from day 21 and this is a key aspect in the management of health care personnel (11) and in population immunity studies related to the control of the pandemic (12).

Our study is subject to some limitations. First, it has been conducted in a single hospital. Further multicenter studies are necessary to reinforce our findings. Second, the selection of patients was made according to the diagnostic needs of our hospital. Consequently, group 3 patients were all patients with negative PCR patients with clinical and radiological criteria of pneumonia and because of that, our results could not be generalized to other patients with COVID-19 and other clinical syndromes. Additionally, group 3 patients also presented a longer evolution time than group 2 patients. This probably explains that the overall positivity rates of the serological test are better than in group 3 (88.9% vs 47.3% in group 2). However, when we focus on patients with 14 or more days from onset of symptoms, the sensitivity and positivity rate increased for groups (91.1% for group 3 and 73.9% for group 2 patients), and this difference was statistically significant. Because all of these limitations, further multicenter studies including all kinds of clinical presentations are needed in order to reinforce our conclusions.

The question about the reliability of serologic rapid tests is still under debate (13) and more research is needed on this topic. We think that our study may help to point out the usefulness of these rapid tests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

Conflict of interest

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The authors declare that they have no conflicts of interest.

Informed consent

Since the present study is retrospective, informed consent was not required.

Ethical approval

The study was conducted according to the ethical requirements established by the Declaration of Helsinki.

The Ethics Committee of Hospital Universitario Príncipe de Asturias (Madrid) approved the study.

Author contributions

Study concept and design: FPG, RPT and JCG

Patients' selection and clinical data acquisition: FPG, RPT, JR, TA, PGH and JCG

Sample processing: JR, TA and PGH

Statistical analysis and interpretation of data: FPG and RPT

Writing of the manuscript: FPG, RPT, JR and JCG

Critical revision of the manuscript for relevant intellectual content: JR, JCG

Supervision and visualization: JCG

All authors read and approved the final manuscript.

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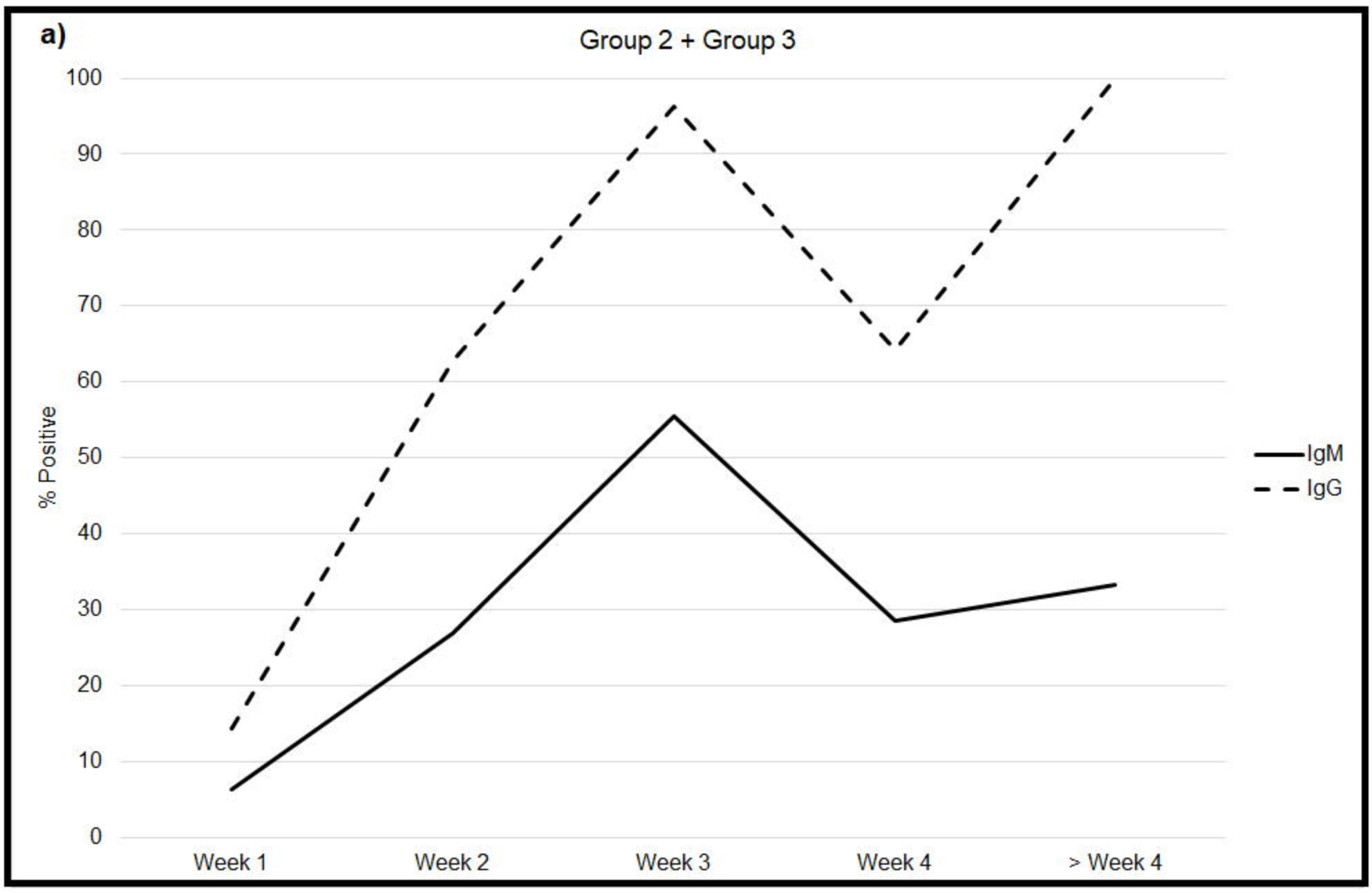

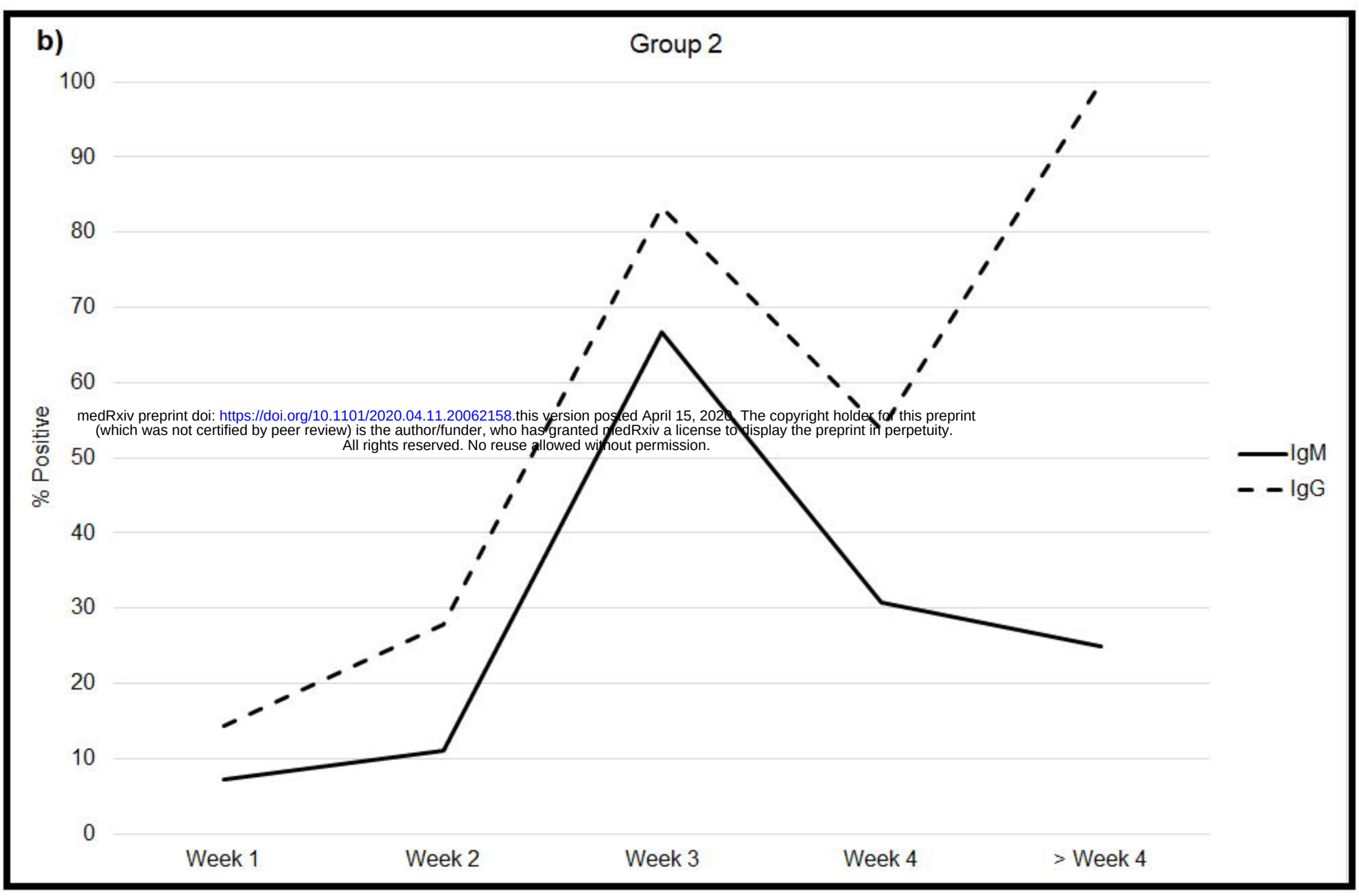

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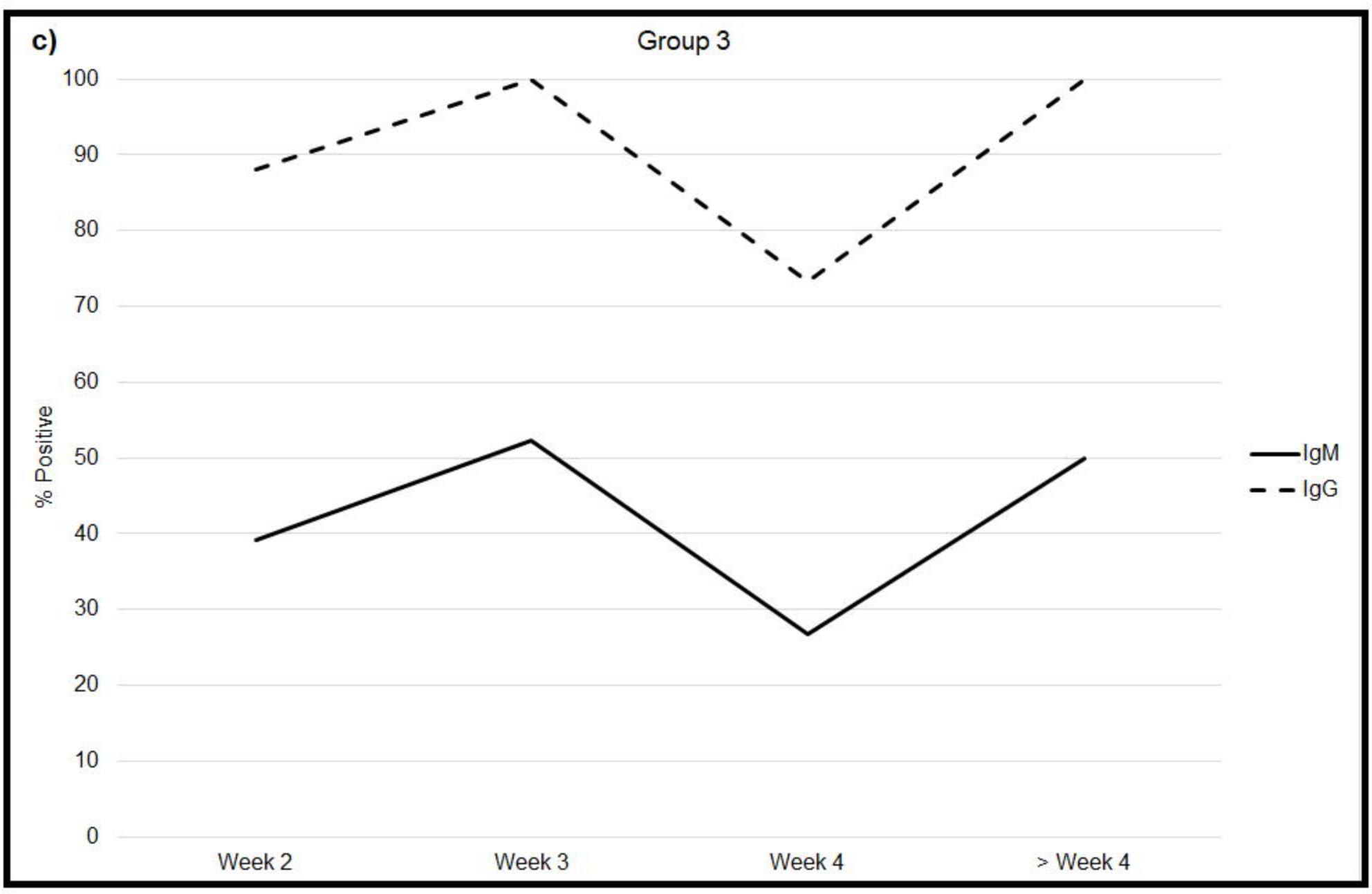

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