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**Serum IgG concentrations in adult patients experiencing virus-induced severe asthma exacerbations**

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**Abstract:**

Background: Patients experiencing severe asthma exacerbations have a poorer quality of life and an increase in morbidity and mortality. Viruses are frequently involved in asthma exacerbations.

Objective: Determining the value of measuring serum immunoglobulin G (IgG) concentrations in asthma exacerbations and their link with viral infections in patients hospitalised for asthma has been assessed.

Methods: Patients hospitalised for asthma exacerbation were included in an observational study from the 1 January to 31 December 2015. Serum IgG concentrations on admission were compared between patients with a positive upper airway viral sample to those with a negative viral sample.

Results: Amongst the 82 patients included, those with positive viral nasopharyngeal samples (n=40) presented with lower serum IgG concentrations during exacerbation than those with a negative viral sample (n=42) ( $10.1 \pm 2.3$  g/l vs.  $11.5 \pm 3.6$  g/l,  $p < 0.05$ ). The median concentration of serum IgG was lower in patients hospitalised for more than three days compared to those hospitalised for less than three days ( $10.0$  g/l [8.2-12.4] vs.  $11.4$  g/l [10.1-12.8],  $p < 0.05$ ) and in patients who received oral corticosteroid therapy for more than five days compared to those treated with oral steroids for less than five days ( $10.1$  [8.3-12.2] vs.  $11.6$  g/l [10.0-13.8],  $p < 0.05$ ).

Conclusion: Serum IgG was significantly lower when asthma exacerbations were associated with positive viral samples. The patients with lower serum IgG concentrations required longer hospitalisations and longer courses of steroids.

Highlights

What is already known about this topic? Many patients suffering from asthma experience virus-induced asthma exacerbations but the pathophysiology is not fully understood and no biomarkers have been found to predict severity.

What does this article add to our knowledge? Patients hospitalised for asthma exacerbations associated with a positive virus sample have lower serum IgG than their negative counterparts. Longer hospital stays and a longer duration of oral steroids were linked to lower serum IgG concentrations.

How does this study impact current management guidelines? Serum IgG quantification during asthma exacerbations may be lower in patients with positive virus samples but more data are needed.

Key words: asthma, immunoglobulin G, virus, exacerbation

Abbreviations:

ACT: Asthma control test

BMI: Body mass index

CVID: Common variable immune deficiency

COPD: Chronic obstructive pulmonary disease

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

GINA: Global Initiative for Asthma

Ig: Immunoglobulin

IgG: Immunoglobulin G

IgE: Immunoglobulin E

PCR: Polymerase Chain Reaction

ROC curves: Receiver operating characteristics curves

RSV: Respiratory syncytial virus

## **Introduction**

Asthma is a chronic respiratory disease associated with airway inflammation (1). This disease affects approximately 334 million people worldwide and its prevalence is increasing (2). According to the latest World Health Organization (WHO) estimates released in December 2016, there were 383,000 asthma-related deaths in 2015 (3). The majority of these deaths occurs in low- and middle-income countries (3).

Exacerbations play an important role in asthma morbidity and mortality (4). An exacerbation is defined as acute or sub-acute episodes of progressive worsening respiratory symptoms (5). A severe exacerbation corresponds to an emergency consultation or hospitalisation (6). Asthma is an increasingly common cause of emergency department consultations (7). Twenty percent of asthma patients have experienced exacerbations requiring treatment within the emergency department or hospitalisation and these patients account for more than 80% of the total direct costs of asthma (8). Mortality amongst patients hospitalised for asthma exacerbations accounts for one-third of all asthma-related deaths (9).

Infections with pulmonary tropism are very frequently involved in triggering asthma exacerbations (40 to 80% of cases) (10) and are more often associated with failure of conventional treatments in asthmatic patients (11). Rhinovirus, human metapneumovirus, enterovirus, coronavirus and respiratory syncytial virus (RSV) are the most common viruses found in asthma exacerbations (12). Rhinovirus is particularly related to asthma exacerbations and is found in 60% of children experiencing asthma exacerbations (12). In adults, rhinovirus also seems to be frequently involved in asthma exacerbations (13).

Regarding virus-induced asthma exacerbations, the antiviral response is complex and involves immune cells leading to the release of inflammatory mediators (14, 15). Immunoglobulins (Ig) play a key role in the anti-viral response but knowledge remains limited about their

involvement in virus-induced asthma exacerbations. Interestingly, it has recently been shown that patients with primary hypogammaglobulinemia are more likely to suffer from viral infections, including rhinovirus, compared to healthy subjects, in spite of intravenous immunoglobulin replacement (16). The prevalence of asthma appears to be higher in patients with various immune deficiencies including hypogammaglobulinemia, with an estimated prevalence of 15% in the studies (17). The mechanism causing the increased prevalence of viral infections in patients with hypogammaglobulinemia is unknown. Secretory IgA deficiency in the bronchial mucosa has been suggested (16). To our knowledge, the link between viral infections and serum immunoglobulin in asthmatic patients is poorly understood.

The purpose of this project is to compare the serum immunoglobulin G (IgG) concentrations between patients with an upper airway specimen that tested positive for a virus to those with a negative viral specimen at the time of hospitalisation for asthma exacerbations.

## **Population and Methods:**

### **Population**

An observational study was conducted from 1 January to 31 December 2015. Patients with asthma were recruited from the Department of Respiratory Medicine of the University Hospital of Tours, located in the centre of France, as well as from the Department of Respiratory Medicine of the University Centre of Reunion, a French island located in the Indian Ocean. The socioeconomic statuses of the patients are very close because both locations are managed in the same way by the French government. Inclusion criteria were patients aged 18 or older and hospitalised for an asthma exacerbation. An exacerbation was

defined as the increase in respiratory symptoms for more than 24 hours or the use of oral corticosteroid therapy. Asthma diagnoses were established on a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and coughing associated with variable expiratory airflow limitation prior to hospitalisation according to the Global Initiative for Asthma (GINA) (1). Exclusion criteria were smoking more than ten packs of cigarettes a year, chronic obstructive pulmonary disease and pregnancy. The study was approved by the Institutional Review Board of the *Société de pneumologie de langue Française*. Each patient gave an informed written consent to take part in the study.

#### Clinical and biological data during asthma exacerbation

Demographic data such as age, sex, body mass index, smoking status quantified in packs per year (P/A), inhaled treatment prescribed prior to exacerbation, as well as the use and duration of oral steroids during the exacerbation were collected. The total serum immunoglobulin E (IgE) concentration (immunoassay technique, ImmunoCAP IgE total, Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden), blood eosinophilia (Beckman Coulter LH 780 controlled analyser), and C-reactive protein (CRP) (Beckman Coulter LH 780 Controlled Analyser) were also collected. The severity of exacerbations was characterised by the length of the hospital stay including the time spent in the emergency room and if the patient needed to be treated in the intensive care unit. Controlled asthma was defined as an asthma control test (ACT) score greater than or equal to 20 points in the month preceding the consultation.

#### Upper airway viral sampling



Viral carriage was assessed in the nasopharyngeal fluid obtained by nasopharyngeal aspiration performed as soon as possible by qualified nurses accustomed to the technique. The viral identification was performed by multiplex real time Polymerase Chain Reaction (PCR) (Tours: Anyplex II RV16, V1.1 detection, Eurobio, France and Thermal Cycler, C1000, BioRad, US Meeting; Reunion: FTD Respiratory pathogens 21, Fast track diagnostics, Luxembourg and Rotor-Gene Q instrument, Qiagen, France). At least 16 viruses (RSV A and B, Rhinovirus, metapneumovirus, myxovirus influenzae A, H1N1, B, parainfluenzae from 1 to 4, coronavirus 229E, NL63 and OC43, adenovirus, enterovirus) were analysed in each centre. In Reunion, the panel of viruses also included coronavirus HKU1, bocavirus and parechovirus.

#### Immunoglobulin G (IgG) serum concentration

Serum IgG concentrations and IgG subclasses were measured by the nephelometric technique on BN Prospect® (Siemens Healthcare Diagnostics, Marburg, Germany) at the time of admission to the hospital section.

#### Follow-up visit

Patients received a follow-up visit three months after exacerbation. Functional respiratory tests were performed via flow-volume curves using a plethysmograph (SensorMedics Vmax Encore, Carefusion, San Diego, CA). The values of both forced vital capacity (FVC) and forced expiratory volume in one second (FEV 1) were expressed as a percentage of predicted values according to age, sex, weight and height. Airway obstruction was defined by a post-bronchodilator FEV1/FVC ratio of less than 70%. Measurements were taken according to

ATS/ERS 2006 recommendations using the predicted values published by the ERS (18, 19). Prick tests to aeroallergens (house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* at both sites and *Blomia tropicalis* in Reunion)), mould (*Alternaria alternata*), animal dander (cat and dog), cockroaches (*Blattella germanica*), tree pollens (olive tree, birch) and herbaceous plants (ragweed, ambrosia, wormwood and grasses) were also carried out.

## Statistical analyses

Quantitative data, with a normal distribution, were expressed as mean and standard deviation (mean  $\pm$  SD) and quantitative data, with no normal distribution, were expressed as median deviation [interquartile range]. Qualitative data were expressed as frequencies (%). A Student's t-test (parametric) was used to compare continuous variables with normal distribution. The Mann-Whitney test was used for quantitative data and had no normal distribution. Statistical significance was defined as a p value of  $<0.05$ . Receiver operator characteristics (ROC) curves were used to assess serum IgG concentrations as a potential marker of a positive virus specimen. The best IgG cut-off was determined using the Youden's index. Sensitivity and specificity of IgG cut-off for a positive virus sample were also defined. A Spearman test was used to assess the correlation between serum IgG concentrations and other continuous variables. The linearity of these relations was then tested using linear regression. The statistical analysis was carried out using the Graph Pad Prism 5 software (license reference: GPW6-222441-RILS-2C3D1).

## Results

#### Characteristics of patients and virus distribution:

Eighty-two patients were included in this study. The patients' characteristics are summarised in Table 1. The median age was 49.5 [28.8-63.3] years old. Patients were predominantly female (76.8%) and overweight with a median body mass index (BMI) of 26.3 [22.1-31.2] kg/m<sup>2</sup>. Inhaled corticosteroid treatment was used in 61% of patients before asthma exacerbation and 14.6% out of all the patients required intensive care at the time of exacerbation. The median duration of oral corticosteroid therapy and the median length of stay for the exacerbation were 7.0 days and 4.0 days, respectively.

Nasopharyngeal aspirations were positive for viruses in 48.8% of patients. The most common viruses were rhinovirus (38%), myxovirus influenza (18%), metapneumovirus (12%) and enterovirus (10%) (Figure 1).

#### Characteristics of patients according to the viral status of nasopharyngeal aspiration:

Patients with a positive or negative viral sample showed no statistically significant difference in terms of demographic and biological data (Table 2). Patients with positive nasopharyngeal aspiration for viruses were slightly younger than patients with negative nasopharyngeal aspiration for viruses (43.5 vs. 50.5 years, respectively) with no statistical significance ( $p > 0.05$ ). Patients with positive viral specimens also seemed to be hospitalised in intensive care units more often compared to patients harbouring negative viral specimens (20% vs. 9.5%, respectively), however the difference was not significant.

#### Immunoglobulin blood concentration:

Patients with a positive viral sample had significantly lower serum IgG concentrations than patients hosting a negative viral specimen ( $10.1 \pm 2.3$  g/l vs.  $11.5 \pm 3.6$  g/l,  $p < 0.05$ ) (Table 3). No difference was found for serum IgA and IgM concentrations in both groups. IgG subclasses were similar between groups. An inverse correlation was observed between age and serum IgG concentrations ( $p = 0.016$ ). No other correlation was shown for the other demographic characteristics.

#### Serum IgG concentrations and diagnosis of a positive virus sample.

ROC curve analysing the serum IgG concentrations as a marker for predicting a specimen positive for a virus is presented in Figure 2. According to Youden's index, the best cut-off value of serum IgG to predict a positive virus sample is 12.30 g/l, the optimal sensitivity and specificity were 80.0% and 40.5%, respectively.

#### IgG concentration and characteristics of asthma exacerbation:

The median serum concentration of IgG was significantly lower in patients hospitalised for more than three days than in those whose hospital stay was less than or equal to three days ( $10.0$  g/l [ $8.2-12.4$ ] g/l vs.  $11.4$  g/l [ $10.1-12.8$ ] g/l,  $p < 0.05$ ) (Figure 3B). Patients receiving oral corticosteroids for more than five days had lower median serum IgG concentrations than patients who were given corticosteroid therapy for five days or less ( $10.1$  [ $8.3-12.2$ ] g/l vs.  $11.6$  [ $10-13.8$ ] g/l respectively,  $p < 0.05$ ) (Figure 3C). The median serum concentration of IgG was not significantly different if patients were hospitalised in intensive care units or not (Figure 3A). An inverse correlation was observed between the length of stay and the serum IgG concentration ( $p = 0.022$  with the Spearman test) (Figure 4). No correlation was found between oral steroids and serum IgG concentrations. ROC curves have been created according to the length of stay and the steroid duration in order to know the reliability of serum IgG

concentrations as a predictive biomarker of exacerbation severity. For the length of stay prediction ( $\leq 3$  days or  $> 3$  days), the best sensitivity and specificity of IgG concentrations are 80.00% and 50.00%, respectively for a cut-off value of 11.05 g/l (Figure E1a). Regarding the steroid duration prediction ( $\leq 5$  days or  $> 5$  days), for a cut-off value of 9.99 g/l, the best sensitivity and specificity of IgG concentrations are 62.07% and 66.67%, respectively (Figure E1b). If a positive virus sample is combined with the IgG serum concentrations, for a cut-off of 10.75 g/l, the best sensitivity and specificity of the length of stay prediction are 79.17% and 61.11%. Regarding a cut-off of 11.05 g/l, the best sensitivity and specificity of the steroid duration prediction are 82.76% and 55.00% (Figure 5).

## **Discussion:**

Asthma patients with a positive nasopharyngeal viral sample had a lower serum IgG concentration, at the time of exacerbation, than those with a negative viral sample. Moreover, the median serum IgG concentration was lower in patients hospitalised for more than three days as well as in those who were given oral steroids for more than five days compared to their counterparts.

In our study, the epidemiology of viruses found in patients hospitalised for asthma exacerbations was similar to data observed in the literature. Indeed, herein, rhinovirus was the most frequently observed pathogen (38%). This virus is known to be more often associated with asthma exacerbations in children (20-22), and some works suggest that it is also the most incriminated virus in severe asthma exacerbations in adults (13, 23, 24). Our patients also presented with other viruses such as myxovirus influenzae. Myxovirus influenza, particularly influenza A H1N1, is responsible for a significant morbidity and mortality in asthmatic patients (25-27). Enterovirus appears to be less frequently found in the literature (28). In our

cohort, enterovirus was always found in co-infection with rhinovirus and this represented five out of ten patients who had co-infections. The five remaining patients were co-infected with rhinovirus/myxovirus influenza A (n=3), metapneumovirus A and B/myxovirus influenza A H1N1 (n=1), adenovirus/myxovirus influenza A (n=1) and Coronavirus 229E/myxovirus influenza A (n=1). No relationship between co-infection and serum IgG concentrations or the severity of exacerbations was found.

No demographic differences were found between the patients with positive virus samples and those with negative virus samples. However, although the difference was not statistically significant, patients with a positive virus sample were slightly younger compared to their negative counterparts (43.5 vs. 50.5 years, respectively). The lack of significance is probably due to the small sample size. It is well known that asthma exacerbation in young people is associated with virus infections (29). BMI appears to be a bit higher in patients with positive virus samples compared to patients with negative virus samples (29 vs. 25 kg/m<sup>2</sup>, respectively) but the difference is also not significant. The risk of viral infections in asthma and obese patients has been identified elsewhere in the literature. Indeed asthma and obesity have been found as independent risk factors of pandemic influenza hospitalisation (30). In our study, more patients in the positive virus group required intensive care although there was no significant difference. Data from the literature suggest that respiratory viruses may trigger severe asthma exacerbations, particularly in young people (31).

The link between viral infections and asthma exacerbations is widely recognised and the impairment of viral immunity may partly explain the development of viral infections in asthma patients (32, 33). In influenza infections, IgG has been identified as being particularly involved in protecting the respiratory tract against viruses and its role seems to be superior to IgA (34). Rhinovirus-specific IgG appears to prevent and control re-infection and a high

concentration of specific IgG antibodies is correlated with the attenuation of respiratory symptoms and a reduction in viral shedding (35). A decrease in specific viral antibodies in patients with asthma has been suggested (36). However, in another study, higher antibody responses to rhinovirus have been shown in asthmatic patients compared to non-asthmatic controls (37). Given the study conducted by Johnston et al. on rhinovirus involvement in asthma exacerbations in children, we may also speculate that the admitted patients had less exposure to school-aged children in the past and therefore had not generated a sufficient antibody response to the current virus(es) (38). Other mechanisms beyond adaptive immunity dysfunction are involved in virus-induced asthma exacerbations. Indeed, an altered innate immune anti-viral response has been observed in asthmatic patients compared to non-asthmatic ones (39-41). Our study does not add a mechanistic explanation for the low level of serum IgG in patients with a positive virus sample.

Our results may suggest that serum IgG concentrations at the time of asthma exacerbation would be a marker of severity. Indeed, patients with a hospitalisation length of more than three days or a steroid course of more than five days show lower IgG concentrations at the time of exacerbation. Amongst patients with stable COPD, reduced total IgG levels have been linked to an increased risk of exacerbations and hospitalisations (42). In that study, patients with serum IgG <7 g/l had a higher risk of COPD exacerbations compared to patients with the highest quartile of serum IgG.. We assessed the predictive ability of serum IgG concentrations as a biomarker of exacerbation severity. However, it does not seem to be a useful predictor based on modest sensitivity and poor specificity. If we combine serum IgG concentrations and a positive virus sample, the prediction of exacerbation severity was not improved, and further studies are needed to specifically assess IgG level as a marker of severity in asthma exacerbations. The prediction of next hospitalisations with IgG levels would also be interesting but we cannot answer this question with our study as it was not

designed to answer this question. However, we may speculate that a low IgG level particularly at baseline would predispose patients to virus infection and consequently increase their risk of hospitalisation.

Our study does have several limitations. The difference in IgG concentrations between patients with positive and negative viral samples is statistically significant, but it remains uncertain whether this difference is clinically relevant or not. More robust studies on the role of IgG are needed. In addition, the change of IgG concentrations or other immunoglobulins over time was not assessed in our study. We did not measure IgG in patients in a stable condition. It would have been interesting to know if the IgG decline is transient or longer-lasting. Indeed, in patients with chronic obstructive pulmonary disease (COPD), low IgG serum concentrations at baseline seem to be associated with more severe exacerbations per year (42). However, in this study, no virus analysis was performed. Finally, our study is based on multiplex PCR for virus identification. Nevertheless, the list of viruses, though very extensive, is not exhaustive, therefore emerging viruses cannot be ruled out.

### **Conclusion:**

The results of our study show that serum IgG was significantly lower when severe asthma exacerbations were associated with a positive viral sample. Serum IgG levels were lower in patients with a longer length of stay and when a course of oral steroids was prescribed for a longer duration. Further studies are requested to know the exact usefulness of IgG concentrations as a severity marker of severe asthma exacerbations. The understanding of immunological mechanisms of viral infection in severe asthma exacerbations may be an interesting lead for the development of new therapies in patients for whom severe exacerbations are a source of significant morbidity and mortality.



344

345 Figure 1: Details of viruses found in nasopharyngeal aspirations of hospitalised patients for  
346 asthma exacerbation.

347 Figure 2: Receiver operating characteristics (ROC) curve analysis of serum IgG  
348 concentrations for the prediction of a positive virus sample. At the cut-off value of 12.30 g/l,  
349 sensitivity and specificity are 80.0% and 40.5%, respectively.

350 Figure 3: Comparison of blood IgG concentrations a) between hospitalised patients in  
351 intensive care and those without ICU, b) between patients hospitalised for three days or less  
352 and those hospitalised for more than three days and c) between patients treated during five  
353 days or less with oral corticosteroids and those treated during more than five days, \* $p < 0.05$ .  
354 ICU: Intensive care unit.

355 Figure 4: Scatter plots with regression line showing the relationship between the serum IgG  
356 concentrations and the hospital length of stay. \* $p = 0.0058$  using linear regression.

357 Figure 5: Receiver operating characteristics (ROC) curve analysis of serum IgG  
358 concentrations combined with a positive virus sample for a) the prediction of a length of stay  
359 duration of more than three days (for a cut-off value of 10.75 g/l, sensitivity and specificity  
360 are respectively 80.0% and 40.5%) and b) the prediction of a steroid duration of more than  
361 five days (for a cut-off value of 11.05, the best sensitivity and specificity are 82.76% and  
362 55.00%).

363

364 Table 1: Characteristics of patients hospitalised due to asthma exacerbations.

	<b>n=82</b>
Age (years)	49.5 [28.8-63.3]
Female	63 (76.8)
Active or former smokers	21 (25.6)
BMI (kg/m <sup>2</sup> )	26.3 [22.1-31.2]
Allergen sensitisation	35 (42.7)
Use of an inhaled corticosteroid before hospitalisation	50 (61.0)
Inhaled corticosteroid dose (beclomethasone equivalent doses) (µg/d)	1600 [800-2000]
Exacerbation ≥2 12 months prior to exacerbation	15 (18.3)
Oral corticotherapy duration for exacerbation	7.0 [5.0-8.5]
Length of hospitalisation	4.0 [2.0-5.0]
Intensive care unit stay at the time of exacerbation	12 (14.6)
Positive viral sampling	40 (48.8)
FEV1 after hospitalisation (ml) (% predicted values)	76 [63-88]
FEV1/FVC after hospitalisation (%)	74 ± 15
Blood Eosinophil (G / l)	0.20 [0.03-0.68]
Total IgE (kIU / l)	339 [148-786]

365 Quantitative data, with normal distribution, are expressed as means and standard deviation  
366 (mean ± SD) and quantitative data, without normal distribution, are expressed in median  
367 [interquartile range]. The qualitative data are expressed as frequencies (%).  
368

369 Table 2: Characteristics of patients hospitalised for asthma exacerbations with positive or  
370 negative upper airway viral samples. FEV1: Forced expiratory volume in 1 second, FVC:  
371 Forced vital capacity, IgE: Immunoglobulin E

	<b>Virus + n=40</b>	<b>Virus – n=42</b>	<b>p</b>
Age (years)	43.5 [24.3-60.3]	50.5 [36.0-68.3]	0.14
Female	33 (82.5)	30 (71.4)	0.30
Active or former smokers	11 (27.5)	10 (23.8)	0.80
BMI (kg/m <sup>2</sup> )	29.0 [22.0-33.2]	25.0 [22.3-30.4]	0.42
Allergen sensitisation	18 (45.0)	17 (40.5)	0.82
Use of an inhaled corticosteroid prior to hospitalisation	24 (60.0)	26 (61.9)	1.00
Inhaled corticosteroid dose (beclomethasone equivalent doses) (µg/d)	1600 [800-2000]	1600 [800-1600]	0.91
Exacerbation ≥2 12 months prior to exacerbation	5 (12.5)	10 (23.8)	0.39
Oral corticotherapy duration while exacerbation (days)	7.0 [5.0-9.5]	6.0 [5.0-8.5]	0.15
Length of hospitalisation	4.0 [2.0-5.0]	3.5 [2.0-5.0]	0.31
Intensive care unit stay at the time of exacerbation	8 (20.0)	4 (9.5)	0.22
FEV1 after hospitalisation (% predicted values)	80.5 [61.0-90.5]	75.5 [63.5-86.00]	0.50
FEV1/FVC after hospitalisation (%)	75 ± 12	66 ± 12	0.052
Blood Eosinophil (G/l)	0.2 [0.0-0.4]	0.2 [0.0-0.8]	0.39
Total IgE (kIU/l)	349 [185-1003]	310 [127-516]	0.29

372 Values are expressed as median and [interquartile range] or mean ± standard deviation for  
373 quantitative data and raw values (%) for categorical data. A Student's t-test (parametric) is  
374 used to compare continuous variables to a normal distribution. The Mann-Whitney test is used  
375 for quantitative data that do not have a normal distribution.

Table 3: Comparison of serum Immunoglobulin G (IgG), Immunoglobulin A (IgA), Immunoglobulin M (IgM) and IgG subclass levels between patients with positive viral samples (Virus +) and negative (Virus -).

	<b>Virus + n=40</b>	<b>Virus – n=42</b>	<b>p</b>
IgG (g/l)	10.1 ± 2.3 10.10 [8.15-11.68]	11.5 ± 3.6 11.25 [9.09-13.43]	<0.05
IgA (g/l)	2.30 [1.77-3.06]	2.34 [1.98-2.86]	0.70
IgM (g/l)	0.88 [0.55-1.15]	0.75 [0.56-1.36]	0.91
IgG1 (g/l)	4.9 [3.5-5.8]	5.5 [4.5-7.0]	0.059
IgG2 (g/l)	3.7 ± 1.0	4.1 ± 1.4	0.12
IgG3 (g/l)	0.58 [0.30-0.80]	0.57 [0.43-0.86]	0.38
IgG4 (g/l)	0.27 [0.15-0.43]	0.27 [0.15-0.60]	0.85

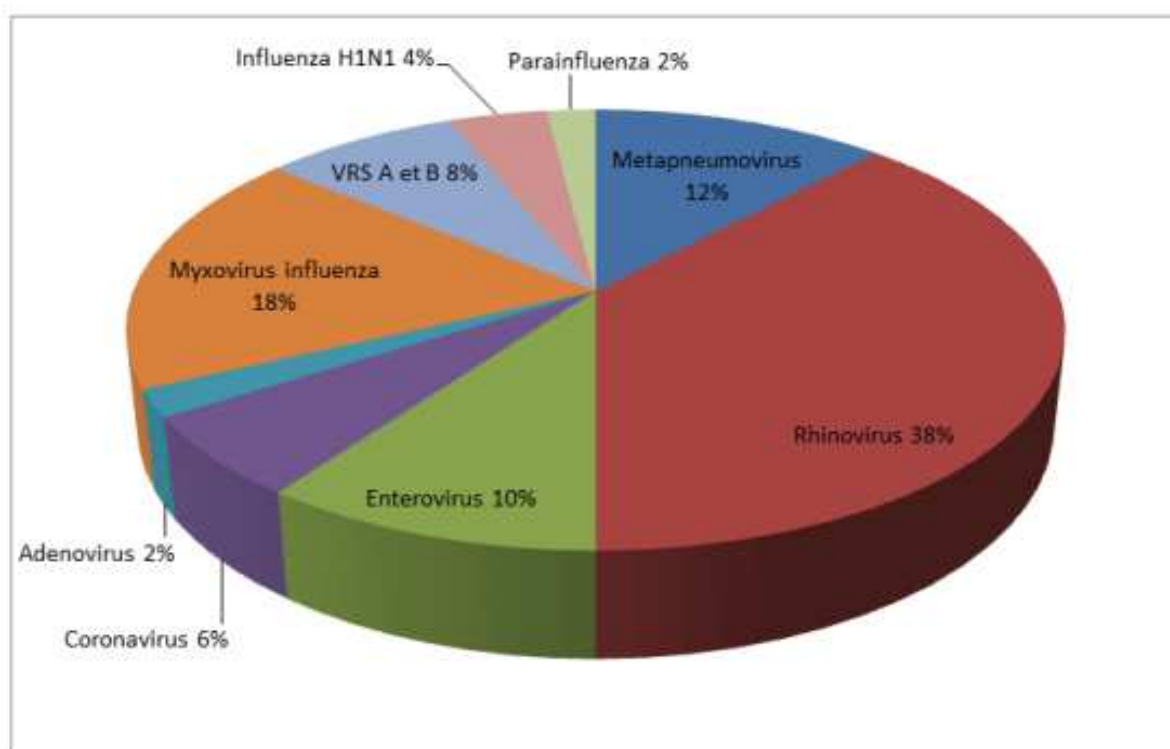
Values are expressed as median and [interquartile range] or mean ± standard deviation for quantitative data and raw values (%) for categorical data. Both median [interquartile range] and mean ± standard deviation are given for IgG. A Student test (parametric) is used to compare continuous variables to a normal distribution. The Mann-Whitney test is used for quantitative data that do not have a normal distribution.

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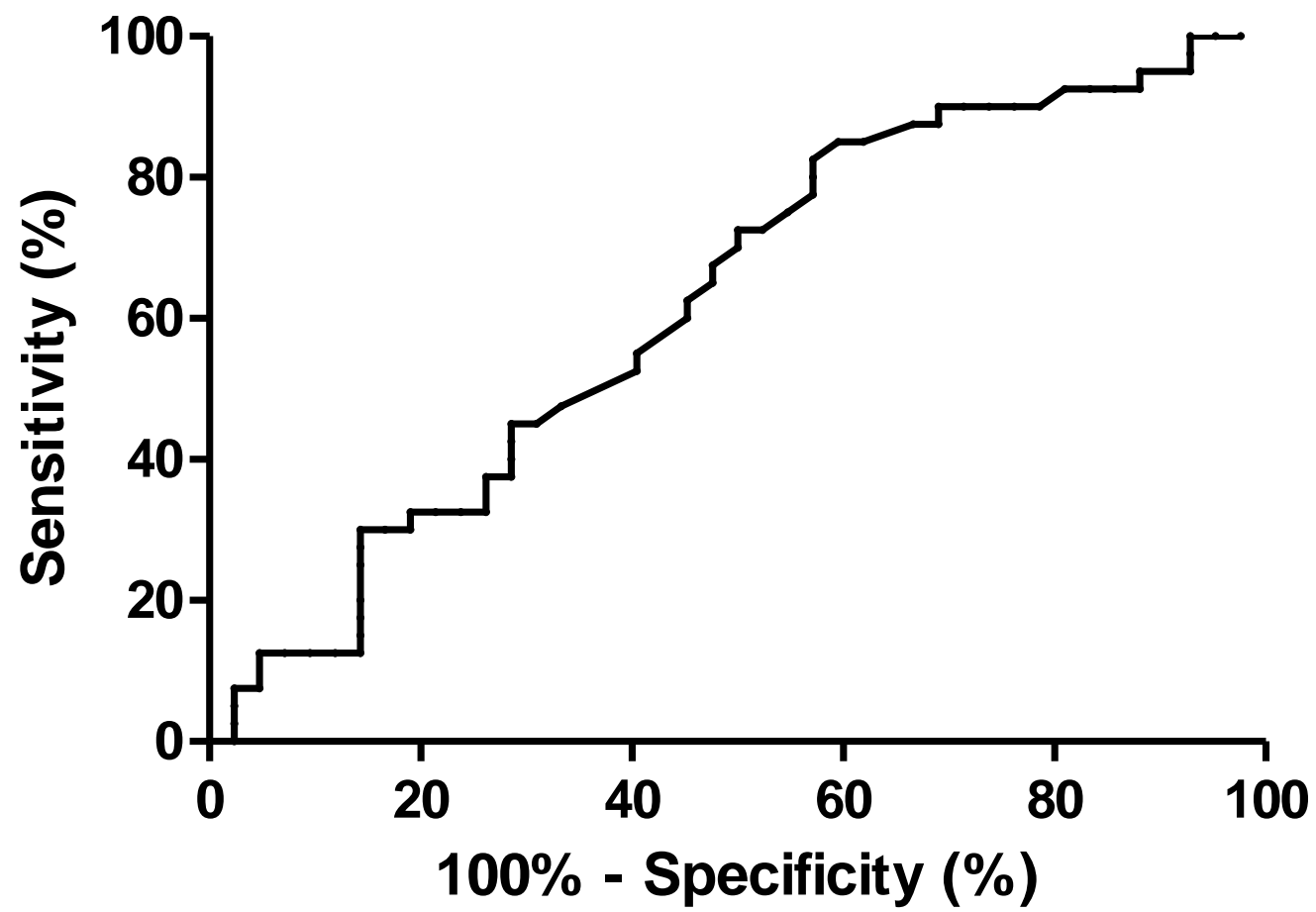
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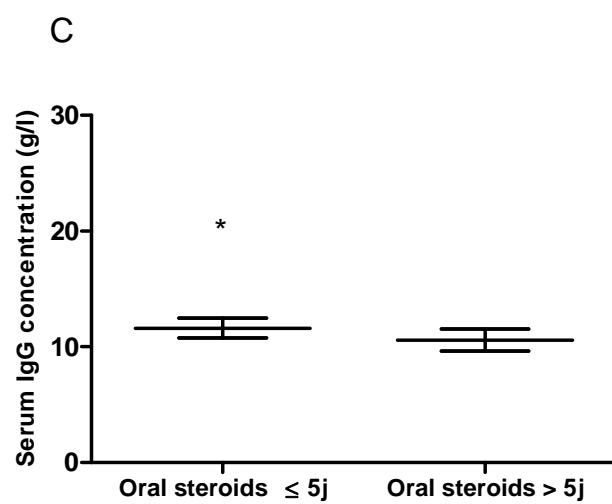
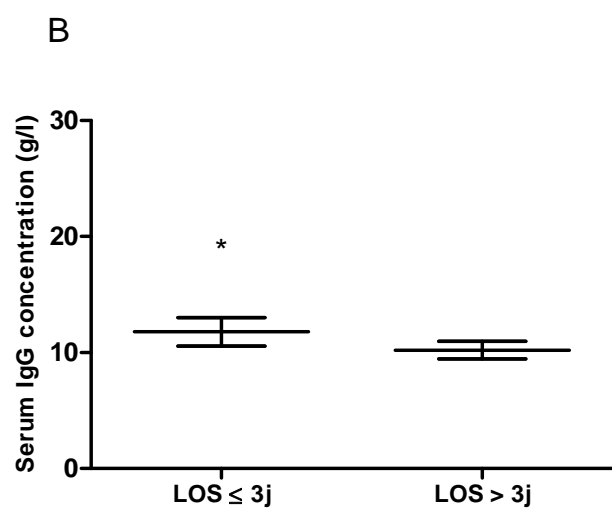
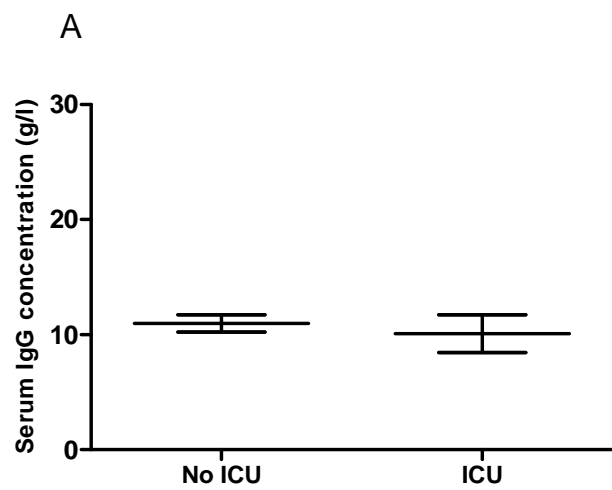
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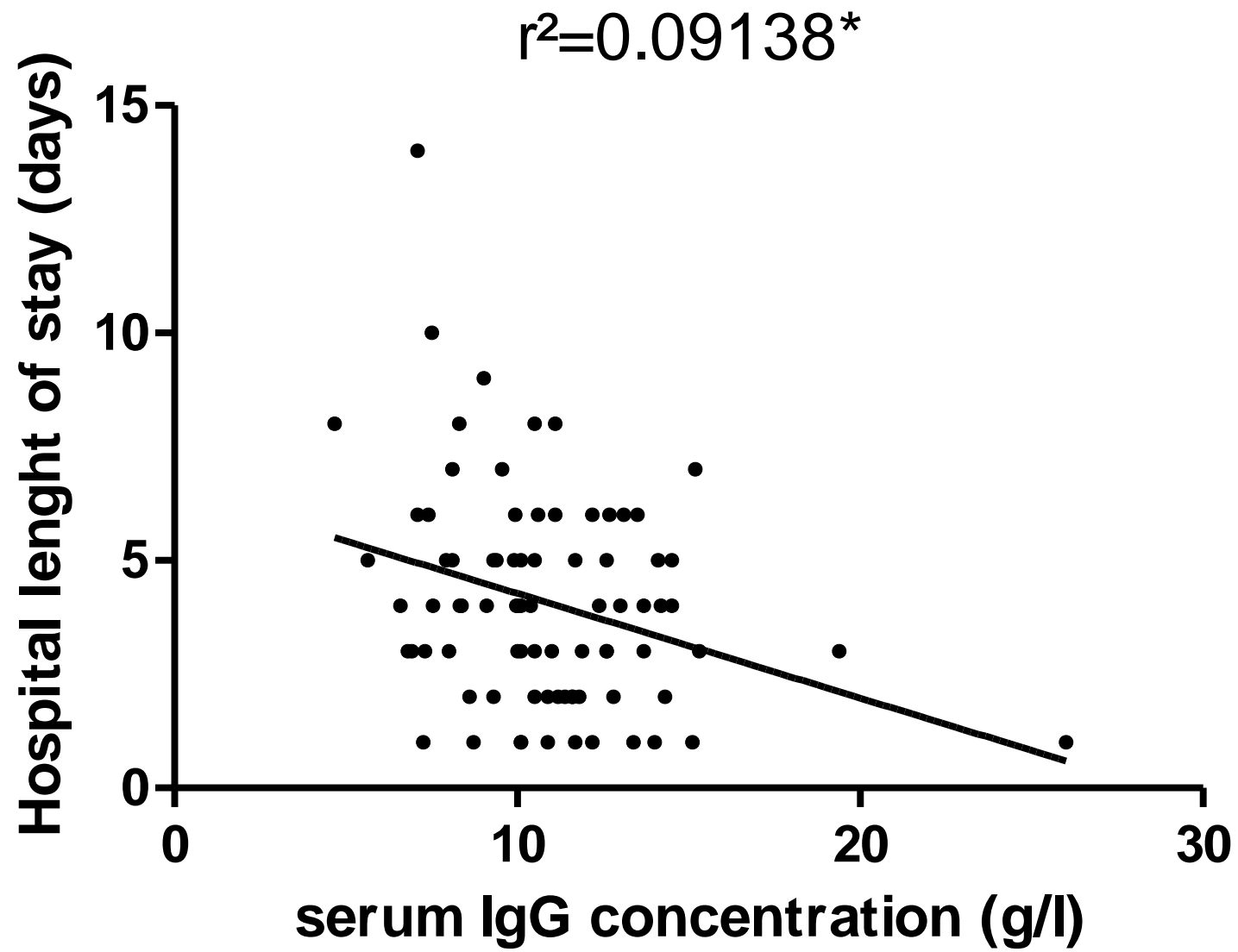
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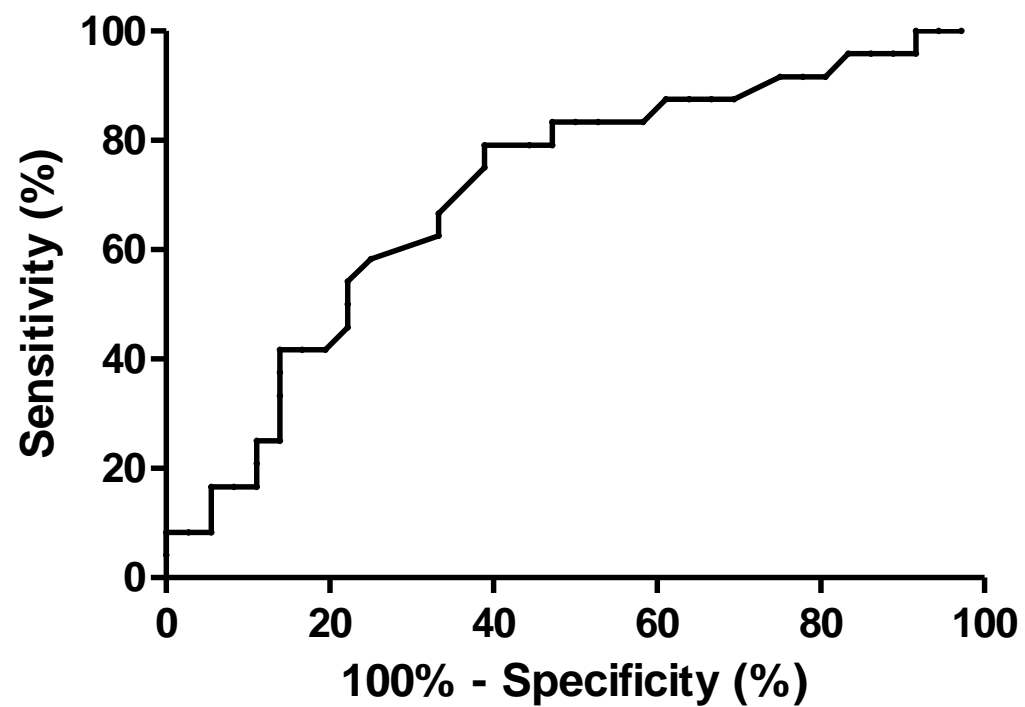








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