



## Research Article

# Platelet Functions as Gender Specific Biomarkers in Kawasaki Disease

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## Abstract

**Background:** Kawasaki disease (KD) is one of the most common pediatric vasculitis that, in absence of adequate treatment, can be complicated by dilations and aneurysms of the coronary arteries. This study was aimed to identify new gender-specific biomarkers predictive of cardiovascular complications. **Methods:** We analyzed 257 KD patients (162 males and 95 females) admitted to the Bambino Gesù Children's Hospital of Rome (Italy) between January 2005 and September 2018. Flow cytometry analyses were used to evaluate platelet functions, while echocardiography was used to detect cardiovascular complications. **Results:** Compared to females, we found that males with KD: i) had a higher rate of cardiovascular complications ( $p < 0.05$ ); ii) were "non-responders" to the first bolus of immunoglobulins and iii) undergo thrombocytosis probably due to a platelet death defect. **Conclusions:** According to literature, this study confirms gender influence in KD course and therapy response, and proposes platelet functions as new sex-associated predictive biomarkers of cardiovascular disease. Male gender could represent a negative prognostic factor for KD and be associated with a high risk to develop cardiovascular complications. The clinical implications of this investigation could be the improvement of first-line corticosteroid therapy and the need for closer echocardiographic follow-up for male patients.

**Keywords:** Kawasaki disease; Gender differences; Cardiovascular complications; Response to therapy; Platelets; Biomarkers.

## Introduction

Kawasaki disease (KD) is one of the most common pediatric vasculitis mainly occurring in children under the age of 5 years [1]. The incidence of KD is consistently higher in males with respect to females (M: F = 1.3-1.8: 1.1). In absence of adequate treatment, KD can be complicated by vascular dilations and coronary artery aneurysms (CAA) [2]. It has been reported that dilations and aneurysms of coronary artery affect 15 - 20% of untreated patients [1] and 2 - 4% of treated ones [3,4].

In the acute phase the standard therapy for KD is based on the intravenous administration of a single high-dose (2 g/kg) of immunoglobulins (IVIG) and high-doses of acetylsalicylic acid (30-50 mg/kg/day) up to 48 hours from the defervescence. This therapy is effective in preventing CAA, when given within 10 days of illness onset. Approximately 10 - 20% of patients have been reported to be refractory to this therapy and require treatment with a second bolus of IVIG, boluses of methylprednisolone or biologic drugs [5]. These "non-responders" patients are at higher risk of coronary artery abnormalities [6].

Therefore, early identification of predictors for IVIG resistance might reduce risk of CAA. In the literature it is reported that white blood cell count, proportion of neutrophils, hemoglobin

(Hb) and C reactive protein (CRP), may be effective predictors for IVIG resistance and CAA in KD patients [7]. This study is aimed to identify new gender-specific biomarkers predictive of cardiovascular complications. Hematological parameters considered risk factor for cardiovascular complications, and platelet functions were analyzed.

## Methods

### Study design and patients

In this retrospective study, 257 KD patients (162 males and 95 females) aged between 1 month and 18 years, admitted to the Bambino Gesù Children's Hospital of Rome (Italy) between January 2005 and September 2018 were analyzed. Patients over 18 years of age and subjects with immunodeficiency were excluded from this study.

Among selected patients, 38.27% of males and 25.24% of females had complications such as vascular dilations and coronary artery aneurysms (Table 1).

Characteristics	Males	Females	p-values
Patients (n and %)	162 (63.04%)	95 (36.96%)	
Age at the onset of diseases (n and %)			
< 1 year	46 (29.3%)	20 (21.5%)	0.176
1-5 years	92 (58.6%)	65 (69.9%)	0.074
> 5 years	19 (12.1%)	8 (8.6%)	0.388
Patients with complications (n and %)	62 (38.27%)	24 (25.26%)	
Mean of days for diagnosis ( $\pm$ DS)	8 ( $\pm$ 2.958)	7 ( $\pm$ 2.634)	0.679

**Table 1:** Characteristics of KD patients at the onset of disease.

This study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki principles for ethical research. Both adult patients and parents of patients under the age of 18 provided informed consent prior to study enrollment. The study was approved by ethics committee of the Bambino Gesù Children's Hospital of Rome (approval number: 1376-OPBG-2017).

### Laboratory measurements

At the onset of the disease patients were subjected to laboratory analyses for the count of white blood cells (WBC), neutrophils, platelets, and mean platelet volume (MPV), C reactive

protein (CRP), ferritin, albumin, and hemoglobin (Hb) levels and echocardiography.

### Platelet isolation

Fresh whole blood samples were collected in acid-citrate-dextrose tubes (ACD; NIH formula A), and immediately centrifuged at 200g for 12 min at room temperature to separate platelet-rich plasma (PRP). Additional ACD was added (one-part ACD per three parts PRP) and platelets were pelleted at 800g for 15 min as previously reported [8]. The isolated platelets contained no detectable erythrocytes and less than one leukocyte per 5000 platelets.

**Evaluation of platelet activation and apoptosis**

Quantitative evaluation of platelet activation was performed by flow cytometry using annexin V binding. Platelet apoptosis was performed by flow cytometry after double staining using fluorescein isothiocyanate-conjugated annexin V and 0.05% trypan blue for 10 min at room temperature and analyzed by fluorescence-activated cell sorting (FACS) in the FL1 and FL3 channels to determine the percentage of dead cells [8].

**Statistical analysis**

Cytofluorimetric results were statistically analyzed by using the parametric Kolmogorov–Smirnov test using Cell Quest Software. A least 20,000 events were acquired. The median values of fluorescence intensity histograms were used to provide a semi-quantitative analysis. Statistical analyses were performed by using Student’s t-test.

For all variables examined the median ± standard deviation (SD) of the general sample and of the two subgroups (male and female group) was calculated. Correlations were evaluated by using Pearson correlation (r correlation coefficient). To test the probability of significant differences, individual group comparisons were evaluated using Bonferroni’s test. All results with p values ≤ 0.05 were considered statistically significant.

The correlation between KD, cardiovascular complications, number of subjects treated with first and second administration of IVIG, and number of subjects treated with steroid therapy, in both male and female, was analyzed by means of the statistical test of chi - square  $\chi^2$ . For the statistical analysis of correlations between 1st bolus of IVIG and some blood parameters we performed the one-way analysis of variance (ANOVA).

**Results**

**Hematological parameters at the onset of KD**

At the onset of disease, among laboratory parameters we focused our attention on variables considered risk factor for cardiovascular complications (CCs). In the blood of KD patients (both uncomplicated and complicated patients) values higher than the reference values were measured for neutrophils, C reactive protein, ferritin, and triglycerides. Conversely, values lower than the reference ones were measured for hemoglobin (Hb) and normal levels were measured for mean platelet count (MPV) and cholesterol levels. For all these parameters, no sex-related differences were detected (Table 2a and 2b). Moreover, a significant (p < 0.05) sex difference was found for platelets count in patients with complications. A mild thrombocytosis was detected only in males.

Parameters	Males (n = 123)	Females (n = 77)	Reference Values	p-values
Neutrophils, median (range)-%,	67.7 (range 92.70-6.90)	67.23 (range 90.50-10.00)	50–60	0.214
Hb, median (range)- mg/dl	11.09 (range 14.5-8)	10.99 (range 13.40–8.30)	11–13	0.833
Platelets, median (range)- number/mm <sup>3</sup>	414.125 (range 653-210)	394.200 (range 734-98)	150-400	0.258
MPV, median (range)-fL	7.6 (range 9.9-5.7)	7.8 (range 10.7-6)	7.5 – 12	0.248

CRP, median (range)- mg/dl	<b>11.48</b> (range 31.93-0.73)	<b>13.80</b> (range 33.74-0.29)	< 0.5–1	0.105
Na, median (range)- mEq/l	136 (range 142-128)	135.57 (range 143-125)	135–148	0.701
Ferritin, median (range)- ng/ml	<b>207.25</b> (range 807-42)	<b>229.9</b> (range 912-53)	13–150	0.895
Albumin, median (range)- g/dl	3.87 (range 5.2-2.1)	3.94 (range 4.7-2,8)	4	0.452
Triglycerides, median (range)-mg/dl	<b>178.36</b> (range 688-60)	<b>180.48</b> (range 563-71)	< 90	0.805
Cholesterol, median (range)- mg/dl	130 (range 237-58)	132.44 (range 220-71)	< 170	0.615

**Table 2a:** Hematological parameters in uncomplicated KD patients at disease onset.

Parameters	Males (n = 39)	Females (n = 18)	Reference Values	p-values
Neutrophils, median (range)-%	<b>63.44</b> (range 90-31.1)	<b>63.89</b> (range 87.8-37.5)	50–60	0.784
Hb, median (range)- mg/dl	10.26 (range 14-7.7)	9.82 (range 11.8-6.5)	11–13	2.018
Platelets, median (range)- number/mm <sup>3</sup>	<b>509.265</b> (range 1171-204)	374.053 (range 941-211)	150-400	<b>0.05</b>
MPV, median (range)-fL	8 (range-10.7-6.3)	8.22 (range 10.5-6.9)	7.5 – 12	0.286
CRP, median (range)- mg/dl	<b>13.48</b> (range 33-1.59)	<b>11.36</b> (range 32.4-1.98)	< 0.5–1	0.225

Na, median (range)- mEq/l	136 (range 142-128)	136.06 (range 141-125)	135–148	0.997
Ferritin, median (range)- ng/ml	<b>231.12</b> (range 812-37)	<b>262</b> (range 884-29)	13–150	0.648
Albumin, median (range)- g/dl	3.67 (range 4.7-2.5)	3.73 (range 4.4-2.1)	4	0.484
Triglycerides, median (range)-mg/dl	<b>167.96</b> (296-78)	<b>174.6</b> (range 357-106)	< 90	0.795
Cholesterol, median (range)- mg/dl	118.64 (range 199-76)	138 (range 221-76)	< 170	0.158

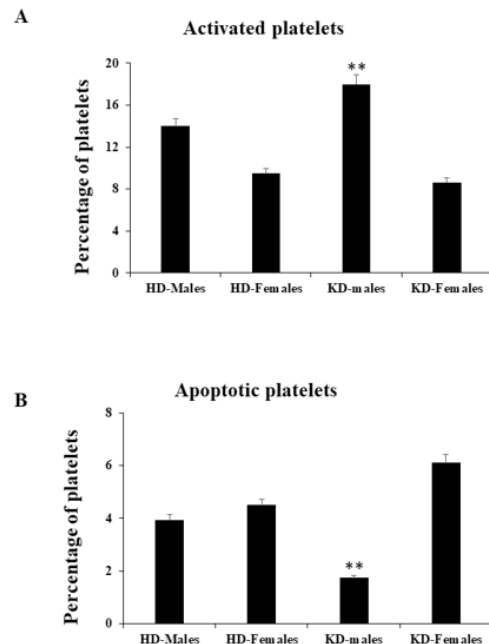
**Table 2b:** Hematological parameters in complicated KD patients at disease onset; Hb = hemoglobin; MPV = Mean platelet volume; CRP = C reactive protein. In bold values higher than the reference range.

### MPV and platelet functions in KD patients

MPV measures platelet size and is considered a marker of platelet activity and a prognostic biomarker of cardiovascular events [9]. In physiological conditions, MPV is inversely proportional to the platelet count, and is associated with hemostasis maintenance [9].

In this study instead, although not significant, a correlation between MPV and platelet count was found in all male and female KD patients ( $\rho = 0.0495$  with  $p = 0.788$  in males and  $\rho = 0.015$  with  $p = 0.906$  in females). This correlation could suggest that a defect of apoptotic process could occur in platelets of KD patients. Based on, the percentage of both activated, and apoptotic platelets was evaluated by flow cytometry. Platelet activation was measured by using the annexin V binding. As shown in (Figure 1A) in males with KD a significant ( $p < 0.01$ ) increase of activated platelets was measured with respect to KD females and to healthy donors (HD both males and females).

Moreover, when a double labeling analysis was performed by using annexin V and trypan blue dye, which labels dead cells, we found that, males with KD had significantly ( $p < 0.01$ ) a lower percentage of apoptotic platelet with respect to KD females and to HD (both males and females) (Figure 1B). This suggests that in males with KD, thrombocytosis could be due to a defect in platelet death. (Figure 1a and 1b)



**Figure 1 (A, B):** Evaluation by flow cytometry of activated (A) and apoptotic (B) platelets; \*\* $p < 0.01$  KD males vs KD females and HD (both males and females).

### Gender differences in patient treatment

Twenty-eight KD patients (18 males and 10 females) did not require any therapy. Instead, 139 (88.53%) males and 83 (89.25%) females with KD were treated with a single bolus of IVIG, with an average day of administration equal to 7 ( $\pm$  3) for males and 7 ( $\pm$  2) for females.

Moreover, 35.5% males and 12.5% females with complications did not respond to therapy and were treated with a 2nd bolus of IVIG with an average day of administration equal to 11 ( $\pm$  5.57) for males and 7 ( $\pm$  5.61) for females. Interestingly, the p-value, relative to the number of males and females treated with the 2nd IVIG bolus, was statistically significant ( $p = 0.0445$ ).

In addition, 15 males and 3 females not responding to the 2nd IVIG bolus were treated with steroids. Among these, 4 males and 3 females not responding to steroids were treated with biological drugs. No gender differences were detected between patients treated with steroid and biological drugs ( $p = 0.2433$  and  $p = 0.9791$  respectively). These data are shown in (Table 3).

Treatments	Males (n = 157)	Females (n = 93)	p-values
No treatment (n and %)	18 (11.46%)	10 (10.75%)	0.863
1st IVIG bolus (n and %)	139 (88.53 %)	83 (89.25%)	0.862
Mean day of administration 1st IVIG bolus ( $\pm$ DS)	7 ( $\pm$ 3.4)	7 ( $\pm$ 2.8)	0.915
2nd IVIG bolus (n and %)	34/139 (24.46%)	11/83 (13.25%)	<b>0.0445</b>
Mean day of administration 2nd IVIG bolus ( $\pm$ DS)	11 ( $\pm$ 5.57)	7 ( $\pm$ 5.61)	0.5329
Steroids (n and %)	15/34 (44%)	3/11 (27.27%)	0.2433
Biological drugs (n and %)	4/15 (2.6%)	3/11 (27.7%)	0.9791

**Table 3:** Patient treatments; IVIG = immunoglobulins.

### Predictors of IVIG resistance and CAD risk

As shown in (Table 4) the correlation between the resistance to the 1st bolus of IVIG and some blood parameters was evaluated. No correlation was found between IVIG resistance and Hb values, lymphocytes % and platelet count.

	Males	p values	Females	p-values
Neutrophils %	$r = 0.176$	$p = 0.024$	$r = 0.133$	$p = 0.01$
CRP (mg/dl)	$r = 0.087$	$p = 0.0040$	$r = 0.2442$	$p = 0.0017$

**Table 4:** Correlation between resistance to 1st bolus of IVIG and some parameters; IVIG = immunoglobulins; CRP = C reactive protein

### Gender differences in the treatment of KD patients with complications

Fifty -five patients (36 males and 19 females) developed CCs consisting in lesions of the proximal tract of the coronary arteries with a Z score  $\geq 2$ . These patients were stratified based on therapy response. Interestingly, as shown in (Table 5) significant gender differences ( $p = 0.038$ ) were found in the number of patients with complications treated with a second bolus of IVIG.

Therapy	Males with CCs (n and %)	Females with CCs (n and %)	p-values
1st IVIG bolus	36 (68%)	17 (32%)	>0.05
2nd IVIG bolus	17 (85%)	3 (15%)	0.038
Steroids	9 (100%)	0 (0%)	>0.05
Biological drugs	2 (100%)	0 (0%)	>0.05

**Table 5:** Gender differences in response to therapy for patients with cardiovascular complications; CCs = cardiovascular complications; IVIG = immunoglobulins.

## Discussion

In the last years gender differences and in particular gender-specific medicine became an interesting research area and a clinical necessity. In several diseases, gender differences appear to involve both the immune, hormonal, and genetic systems [10-12].

Females typically develop higher innate and humoral and cellular immune responses than males [13-16]. They show a greater expression of toll-like receptors (TLR) and a greater phagocyte activity of macrophages, neutrophils and antigen presenting cells [17]. At the same time, females are more prone to autoimmune diseases and have more adverse drug reactions than males [18-20]. In fact, diseases such as Sjögren's syndrome, systemic lupus erythematosus (SLE), autoimmune thyroid diseases or scleroderma are 7-10 times higher in females than in males. In addition, females have more adverse drug reactions than males.

Conversely, compared to females, males have an increased NK cells activity and produce higher levels of pro-inflammatory cytokines, such as IL-6 and TNF-alpha [18]. In addition, diseases such SLE or chronic inflammatory bowel diseases have more severe clinical manifestations in males and worse prognosis [18].

In our study, in accordance with the M: F ratio (1.3-1.8: 1) reported in the literature, in all age groups (< 1 year; 1-5 years; > 5 years) a greater incidence of male patients with an M: F ratio of 1.69: 1 was observed [20-23]. At the onset of the disease, no significant differences in age and laboratory tests were observed between the two sexes. Interestingly, a significant ( $p < 0.05$ ) gender difference on platelets count was found in male KD patients with complications. Moreover, a higher percentage of activated platelets and a lower percentage of apoptotic platelets was found in male KD patients.

The presence of these platelets in "non-responder" patients could promote vascular inflammation and thrombotic events [10]. From a therapeutic point of view, a significant gender difference was observed in the response to the first bolus of IVIG. In fact, compared to females, a higher number of "non-responders" males

were treated with a second bolus of IVIG ( $p = 0.0445$ ).

According to literature data, we found that in both males and females "non-responders", the resistance to first bolus of IVIG correlated with neutrophils percentage and CRP levels.

No correlation was found with the Hb value, lymphocytes percentage and platelets number. Moreover, although these patients had triglyceride levels higher than the reference range, their value did not correlate with resistance to first bolus of IVIG.

Based on the above data we can speculate that the different response to first bolus of IVIG in the two sexes could be due to

- i) Different pharmacological profile, which involves absorption, distribution, metabolism, and elimination of the drug;
- ii) Genetic / hormonal and immune system differences between the two sexes.

Furthermore, although not significant, the incidence of developing cardiovascular complications was higher in males than in females. This lack of significance is probably due to the small number of patients. Furthermore, among the subjects who developed cardiovascular complications, a higher number of males required treatment with a 2nd bolus of IVIG than females. This data proved to be significant ( $p = 0.038$ ).

Our results confirmed the influence of gender in the disease course and in the response to therapy. Therefore, male gender would represent a negative prognostic factor, considering the greater number of males with cardiovascular complications and "non-responders" to the first line treatment.

## Conclusions

Our study suggests that the identification of a score including gender differences would be crucial for risk stratification of developing cardiovascular complications at the time of diagnosis. In addition, we could consider the male gender as a predictor of resistance to IVIG and subsequently of the onset of cardiovascular complication.



The clinical implications of these findings could be improved first-line corticosteroid therapy and shorter echocardiographic follow-up for male patients.

Finally, considering the limited number of subjects analyzed in this study and the relative low incidence of the disease in the general population, multicenter studies and a larger number of patients are needed to increase the significance of the data.

## Declarations

## Acknowledgments

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## Competing interests

The authors declare no conflict of interest.

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For this study no financial assistance was received.

## Availability of data and materials

All relevant data are included in the manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

## Author Contributions

ITJ, ACV, AM, ES conceived, designed and wrote the manuscript; MM, GO and CC edited the data; LG performed the experiments; AV supervised the manuscript. All authors read and approved the final manuscript.

## Institutional Review Board Statement

This study was conducted in accordance with the Helsinki Declaration in addition to the approval from the institutional review board of the Bambino Gesù Children's Hospital of Rome (approval number: 1376-OPBG-2017).

## Informed Consent Statement

Both adult patients and parents of patients under the age of 18 provided informed consent prior to study enrollment.

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