Studying Clinical, Biologic and Echocardiography Criteria to Predict a Resistant Kawasaki Disease in Children

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Background: Resistant Kawasaki disease (KD) represents 10%–15% of KD patients and increases risk of coronary artery abnormalities (CAAs). Different scores exist to predict resistant KD but only in Japanese population, although a French team has recently proposed a new scoring system. The principal objective of this study is to establish criteria to predict resistant KD in our representative French population. The second objective is an attempt to develop a predictive score of resistant KD.

Methods: We conducted a retrospective multicenter study including 2 universities and five secondary hospitals in Eastern France. Patients were included over a period from January 1, 2010 through December 31, 2019. Diagnosis of KD was recorded to the European Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative criteria.

Results: Two hundred two eligible patients had KD and 194 patients were analyzed: 160 sensitive KD and 34 (17.5%) resistant KD. In univariate model, serum sodium <133 mmol/L (odds ratio [OR] 2.97 [1.40–6.45]), hemoglobin level <110 g/L (OR 3.17 [1.46–7.34]), neutrophils >80% (OR 2.36 [1.03–5.25]), C reactive protein level >150 mg/L (OR 4.47 [2.07–10.19]), CAA (OR 3.85 [1.67–8.79]) or myocarditis (OR 6.98 [1.47–36.95]) at the diagnosis were statistically significant, but only serum sodium was an independent factor of resistant KD.

Conclusion: This study shows an association between resistant KD and biologic and echocardiography criteria, but only serum sodium is an independent predictive factor. A score to predict resistant KD could not yet be established.

Key Words: Kawasaki disease, resistant Kawasaki disease, serum sodium, coronary artery abnormality

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Kawasaki disease (KD) is an acute febrile illness of unknown origin concerning, especially children less than 5 years of age. It is associated with vasculitis affecting medium-size arteries. In the European region, the European Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative has adopted the American Heart Association definition criteria for the diagnosis of KD.[1]

The mechanisms underlying the biologic triggers of the KD response have not yet been characterized. The acute phase of KD is often accompanied by an activation of T and B cells.[2] An excess in CD8+ T cell activation and an imbalance in their activation and inhibition seem to be important in KD pathogenesis. It seems that if the level of CD8+ T cell activation is too high, intravenous immunoglobulin (IVIG) resistance may occur.[3] A recent study found that the levels of interleukin (IL)-6, IL-10, TNF-α and IFN-γ were significantly increased in KD children pre-IVIG treatment. This inflammatory mechanism may lead to destruction of the internal elastic vascular lamina, followed by myofibroblast proliferation, which could lead to formation of CAA.

Coronary artery abnormalities (CAAs), aneurysms or dilatations, are the most frequent complications of KD. Approximately, 25% of untreated children develop CAA.[4] Before standardized treatment of KD, CAA was the leading cause of acquired heart disease in children. CAAs are evaluated by echocardiography and Z-score (the internal dimension of the coronary artery expressed as the number of SD units normalized for body surface area) is used for evaluating the severity of coronary artery dilatation. According to Manlhiot et al,[5] a CAA standardized classification is defined by: a simple coronary dilatation for a Z-score 2 to 2.5, small aneurysm for a Z-score ≧2.5 to 5, medium aneurysm for a Z-score ≧5 to 10 and large or giant aneurysm for a Z-score ≧10.

The goal of therapy in KD is to reduce inflammation, arterial damage and prevent thrombosis caused by CAA. The standard therapy is a high single dose of IVIG 2 g/kg with oral acetylsalicylic acid (ASA) moderate or high dose (30–50 or 80–100 mg/kg/d).[6,7] Then, antiplatelet activity (at low dose) of ASA, 3–5 mg/kg/d is begun and continued until the patient has no evidence of CAA. Newburger et al[8] demonstrated that high dose of IVIG administered early in the course of KD was effective in reducing the prevalence of CAA.

Approximately 15%–20% of KD patients develop resurgence or persistent fever 24–48 hours after the end of initial IVIG infusion (SHARE initiative considered 48 hours), named "IVIG resistant," "IVIG unresponsiveness" or "resistant KD."[9,10] In this study, the term "resistant KD" was used. Many studies have shown that resistant KD patients were at an increased risk of CAA.[11–13] Different scoring systems (Kobayashi, Egami and Sano) have been developed but only work in the Japanese population.[14–16] Indeed, these scores are not validated in North American,[17,18] European[19] and Chinese population.[20] There is no consensus for a standard protocol for the management of resistant KD.[21] Resistant KD patients may require additional therapy like cyclosporine, cyclophosphamide, methotrexate,[22] infliximab or corticosteroids therapy.[23,24] The RAISE study has shown that the addition of corticosteroids (prednisolone) to the standard regimen of IVIG improves CAA outcomes in patients with severe KD or the highest risk of resistant KD in Japanese population.[25–27] These data led the SHARE initiative to recommend the addition of corticosteroids in severe KD in Europe.[1] However, a method for predicting resistant KD to an initial course of IVIG has hardly been established in the global population.

Identifying children with a high risk of resistant KD is essential because the proportion of these patients seems to have increased in Japan population from 6.7% to 23.2%[11] and in San

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Diego population from 10%–20% to 38%.[17] We lack data for Europe. The scores previously mentioned do not therefore allow us to predict resistant KD. Very recently, a French team[28] working on the Kawanet study confirmed that the 3 Japanese scores had poor performances in our whole multiethnic French population and proposed a new scoring system.

Consequently, the primary objective of this study was to establish clinical, biologic and echocardiography criteria to predict resistant KD in children with KD in our French population. The second objective was an attempt to develop a predictive score of resistant KD.

MATERIALS AND METHODS

Patients diagnosed with KD according to the SHARE initiative criteria, between 0 to 17 years and 11 months old, were included in this retrospective study over period from January 1, 2010 through December 31, 2019. It was a multicenter study including one university hospital and one other with its 5 secondary hospitals of a whole region in Eastern France. To identify eligible cases, we contacted the Medical Information Department in each hospital who used the CIM-10 classification (M30.3: Adeno-skin-mucous syndrome [Kawasaki]). Children with other diseases that could explain symptoms and deceased patients were nonincluded. Once eligible patients had been identified, their families received a nonopposition information note by postal mail.

Variables included demographic, clinical, biologic and echocardiography data defining complete or incomplete KD, sensitive or resistant KD. Resistant KD was defined as resurgence or persistent fever 48 hours after the end of initial IVIG infusion. Demographics data were defined as age at diagnosis and age <12 months, number of days of fever at diagnosis and KD complete. KD complete was defined by the SHARE initiative criteria: 5 days of fever and at least 4 of 5 clinical features: nonexudative bilateral conjunctival injection, erythema of the lips and oral cavity, polymorphous exanthema, changes in the extremities and nonpurulent cervical lymphadenopathy. Incomplete KD includes 5 days of fever with C reactive protein (CRP) > 30 mg/L and erythrocyte sedimentation rate (ESR) > 40 mm/h, associated with at least 3 of 6 biologic features (anemia, platelets > 450 G/L after 7 days of fever, albuminemia < 30 g/L, high alanine aminotransferase (ALT), leukocytes > 15 G/L, leukocyturia > 10 GB) or CAA.

Clinical data were defined as nonexudative bilateral conjunctival injection, erythema of the lips and oral cavity, polymorphous exanthema, changes in the extremities and nonpurulent cervical lymphadenopathy. Biologic data were represented by the hemoglobin level, platelet count, white blood cell count, percentage of lymphocyts and neutrophils, serum sodium, aspartate transferase (AST), albumin level, CRP level, procalcitonin (PCT) level and ESR. Echocardiography data were collected, including CAA, myocarditis and pericarditis at diagnosis. CAAs have been collected from the echocardiography data by measuring on 2D echography the internal dimension of the coronary artery and then we adjusted these dimensions on the body surface area (Z-scores) using computer software (Parameter(z)). The occurrence of liver abnormality, defined as hydrocholecyst by ultrasound, was also collected. Finally, therapy associated data were collected, such as IVIG and number of cures, corticosteroids therapies and other additional therapies. Data were presented as median, minimal and maximal values for continuous variables or numbers and percentages for categorical variables.

The χ^2 test was used to compare categorical variables and the Student t or Mann–Whitney and Wilcoxon tests were used for quantitative variables. To identify predictors factors of resistant KD, a univariate analysis using the logistic regression model was constructed using demographic data (age in month, days of fever at diagnosis), clinical data (changes in the extremities), laboratory data (serum sodium, hemoglobin level, platelet count, AST, albumin level, percentage of neutrophils and CRP level) and cardiac disease at diagnosis (CAA, myocarditis and pericarditis). The univariate predictors with $P < 0.2$ were entered in a stepwise multivariate logistic regression model. The odds ratio (OR) and their 95% confidence intervals were presented in the final multivariate model. A P value of less than 0.05 was considered significant. All analyses were performed with the use of R version 4.0.0 (R Development Core Team, 2005).

This study procedures conformed to the methodology required in France and was approved by the Clinical Research Delegation of one of the university hospitals.

RESULTS

Of 202 eligible patients, 194 were enrolled in the study: 160 sensitive KD (82.5%) and 34 resistant KD (17.5%). Eight patients were nonincluded: one was deceased of other cause declared after KD (leukemia) and we did not send a nonopposition information note to the parents, 6 did not meet inclusion criteria and 1 declined to participate (Fig. 1).

Table 1 summarizes demographic, clinical manifestations, blood tests, biochemical tests, inflammatory tests, cardiac complications, digestive ultrasound and therapeutic outcomes in both sensitive and resistant KD. We demonstrated a statistical difference between sensitive and resistant KD for type of KD (complete KD 84.4% vs. 100%, respectively; $P = 0.009$), hemoglobin level (114 vs. 103.5 g/L; $P < 0.05$), white blood cell (14.3 vs. 16.8 G/L; $P < 0.001$), percentage of neutrophils (67.8% vs. 75%; $P = 0.036$), albumin level (28 vs. 25 g/L; $P = 0.007$), CRP (107.5 vs. 208.5 mg/L; $P < 0.001$) and ESR (61 vs. 85 mm; $P = 0.017$). CAA developed in 18.1% of patients and significantly more often on resistant KD than sensitive KD (acute phase CAA 38.2% vs. 13.8%; $P = 0.0019$), myocarditis occurred significantly more often on resistant KD than sensitive KD (11.8% vs. 1.9%; $P = 0.019$). The corticosteroids therapies were used significantly more often on resistant KD than sensitive KD (35.3% vs. 5%; $P < 0.001$). Thirty-seven children had ≥2 cures of IVIG: 32 resistant KD and 5 sensitive KD. One resistant KD received another additional therapy by interleukin 1 target drug.

To identify predictive factors of resistant KD, univariate analysis was used with logistic regression. In Table 2, 13 variables were identified: 2 demographic variables (age < 12 months, days of fever < 5 at diagnosis), 1 clinical variable (changes in the extremities), 7 biologic variables (serum sodium, hemoglobin level, platelet count, AST, albumin level, neutrophils and CRP level) and 3 cardiac variables (CAA, myocarditis and pericarditis). Lower serum sodium < 133 mmol/L (OR 2.97 [1.40–6.45]), lower hemoglobin level < 110 g/L (OR 3.17 [1.46–7.34]), higher percentage of neutrophils > 80% (OR 2.36 [1.03–5.25]), higher CRP level > 150 mg/L (OR 4.47 [2.07–10.19]), CAA (OR 3.85 [1.67–8.79]) or myocarditis (OR 6.98 [1.47–36.95]) at diagnosis were statistically significant. Children < 12 months of age, fever < 5 days at diagnosis, changes in the extremities, platelet count < 300 G/L, AST > 100 UI/L, albumin level < 30 g/L and pericarditis were not statistically significant.

Hemoglobin level, serum sodium, albumin level and CRP level were analyzed by multivariate logistic regression in Table 3. The results indicated that only serum sodium <133 mmol/L was statistically significant for resistant KD with OR 2.7 [1.12–6.48]. No scores could be established.

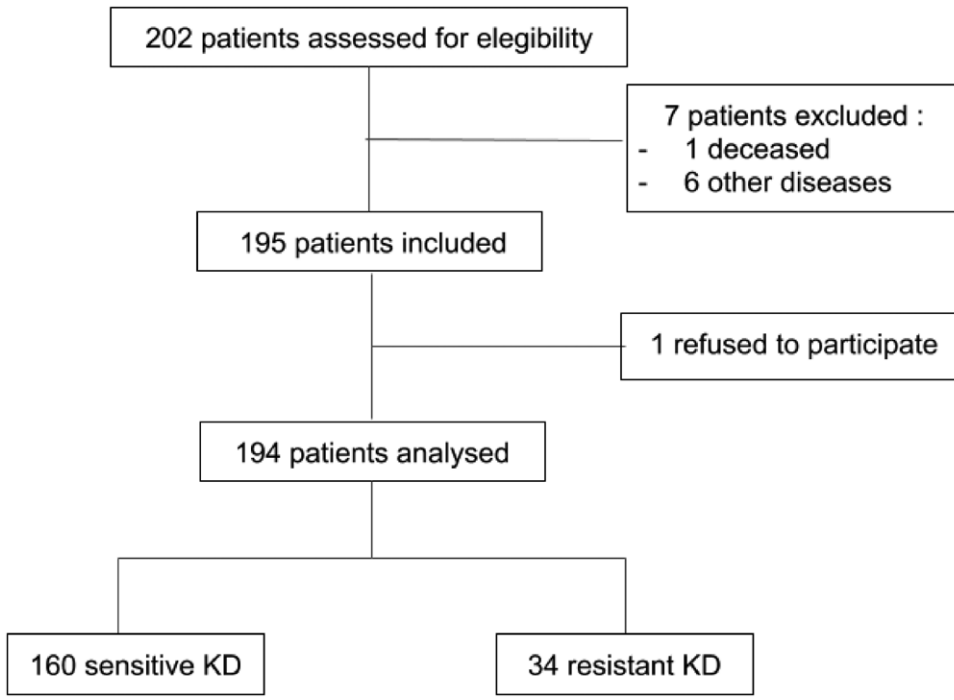

FIGURE 1. Flowchart of the 202 cases of KD.

DISCUSSION

Our study identified biologic and echocardiography factors associated with risk of resistant KD in the univariate model: sodium serum < 133 mmol/L, hemoglobin level < 110 g/L, percentage of neutrophils > 80%, CRP level > 150 mg/L, CAA or myocarditis at the KD diagnosis. Only hyponatremia was an independent factor associated with resistant KD. Our results were similar with independent factors used to predict resistant KD in patients with KD in Japanese population. Kobayashi's score showed that a high percentage of neutrophils ≥ 80% (2 points), AST ≥ 1000 UI/L (2 points), CRP ≥ 100 mg/L (1 point), age ≤ 12 months (1 point), days of illness at initial treatment ≤ 4 (2 points), serum sodium ≤ 133 mmol/L (2 points) and platelet count ≤ 300 G/L were independent risk factors for resistant KD.[29] Egami and Sano scores showed similar factors. These 3 majors' scores do not effectively predict a resistant KD in the European[19] or American population.[18] In San Diego, Tremoulet et al[17] have also proposed a score predictive of resistant KD in a general population. A scoring system developed in a small population in 2006, to predict resistant KD using illness day < 4 (1 point), percentage of bands > 20% (2 points), GGT ≥ 60 UI/L and age-adjusted hemoglobin concentrations ≤ −2 (1 point), had a sensitivity of 73.3% and specificity of 61.9%. At the Beijing hospital, 2 research teams set up predictive scores based on a single center, and this score used polymorphous exanthema (1 point), changes around anus (1 point), days of illness at initial treatment < 4 days (2 points), CRP > 80 mg/L (2 points) and percentage of neutrophils > 80% (2 points).[30,31] One recent French study with a large population (n = 427, Kawanet) identified predictors factors of resistant KD, and a new scoring system, including ALT level > 30 UI/L (1 point), hepatomegaly (1 point), lymphocyts count < 2400/mm^3 (1 point) and time to treatment < 5 days (1 point).[28] They obtained a good sensitivity (77%) and an acceptable specificity (60%). Unfortunately, we could not test it appropriately due to lack of data, especially concerning hepatomegaly. In the univariate model, we have factors in common (eg, CAA, increased CRP or lower serum sodium). However, we did not use the same factors in the multivariate model, possibly due to a difference in recruitment or case definition. First, as authors said in the Kawanet study, their methodology was prospective and their recruitment was voluntary. In our study, we had retrospective methodology but exhaustive population, because all KDs of one region have been recruited. Then, the definition of resistant KD in the Kawanet study was according to the American Heart Association criteria: recrudescent or persistent fever at least 36 hours after the end of IVIG infusion. We followed the SHARE initiative and considered 48 hours.

In our study, neutrophils > 80% and CRP level > 150 mg/L are 2 significant variables in the univariate model that are similar to those in these different scores. Age < 12 months in univariate model, albumin level < 30 g/L, hemoglobin level < 110 g/L and CRP level > 150 mg/L in the multivariate model were not statistically significant but seemed to be associated with a high risk to develop resistant KD. It would be interesting to expand our cohort of resistant KD to increase statistical power and better evaluate these criteria.

We would like to develop other results. First, there is no incomplete KD in our resistant KD population. This observation had already been described that resistant KD is typically.[29] Second, in our study, 18.1% had CAA at diagnosis and CAA was statistically associated with resistant KD. There is an increase in the detection of CAA, from 15% (between 1973 and 1979)[4] to 25% in 2017.[29] This increasing the detection of CAA was explained by Manhiot et al who defined a classification scheme based solely on coronary artery BSA-adjusted Z-scores,[5] and incidence of CAA is different between ethnic groups but we did not study different ethnic groups.[32] We collected CAA at the diagnosis but did not collect CAA over the time. Finally, 5 sensitive KD had second cure of IVIG. We could justify by a different definition of resistant KD (resurgence or persistent fever last 48 hours) or the therapeutic was more aggressive for these children (depending of practitioner).

TABLE 1. Characteristics of the 194 Patients With KD

Variables	Total Population n = 194	Sensitive KD n = 160	Resistant KD n = 34	*P*
Demographics				
Age (months), Median (Min–Max)	34 (2–192)	35 (2–192)	27.5 (3–140)	0.22
Age at diagnosis < 12 months, n (%)	37 (19.1)	27 (16.9)	10 (29.4)	0.15
KD complete, n (%)	169 (87.1)	135 (84.4)	34 (100)	**0.009**
Day of fever at diagnosis, median (Min–Max)	5 (1–30)	5 (1–30)	5 (3–14)	0.17
Clinical manifestations, n (%)				
Polymorphous exanthema	178 (91.8)	145 (90.6)	33 (97.1)	0.31
Nonpurulent cervical lymphadenopathy	172 (88.7)	139 (86.9)	33 (97.1)	0.13
Changes in the extremities	107 (55.2)	84 (52.5)	23 (67.6)	0.106
Nonexudative bilateral conjunctival injection	168 (86.6)	136 (85.0)	32 (94.1)	0.25
Erythema of the lips and oral cavity	165 (85.1)	136 (85.0)	29 (85.3)	0.97
Blood tests, median (Min–Max)				
Hemoglobin level (g/L)	113 (66–198)	114 (66–198)	103.5 (73–130)	**<0.001**
Platelet count (G/L)	360 (36–1340)	357 (43–1340)	395.5 (36–1270)	0.31
White blood cell (G/L)	15 (3.6–38)	14.3 (3.6–33)	16.85 (0.8–38)	**0.003**
Lymphocyts (%)	20 (1–78)	20.9 (1–78)	17.2 (2–60)	0.11
Neutrophils (%)	69 (12–96)	67.8 (12–96)	75 (30–96)	**0.036**
Biochemicals tests, median (Min–Max)				
Serum sodium (mmol/L)	135 (123–144)	135 (123–144)	133 (128–141)	0.13
AST (UI/L), n = 184	32 (9–424)	32 (9–424)	34 (14–160)	0.67
Albumin level (g/L), n = 128	28 (15–41)	28 (15–41)	25 (15–37)	**0.007**
Inflammatory factors, median (Min–Max)				
CRP (mg/L)	116 (<0.1–534)	107.5 (<0.1–347)	208.5 (8–534)	**<0.001**
PCT (µg/L), n = 117	1.6 (00.8–144)	1.39 (0.08–144)	2.7 (0.3–81.9)	0.32
ESR (mm), n = 70	64.5 (6–110)	61 (6–109)	85 (34–110)	**0.017**
Cardiac complications, n (%)				
Coronary artery abnormality (Z-score ≥ 2.5), n = 193	35 (18.1)	22 (13.8)	13 (38.2)	**0.0019**
Myocarditis, n = 193	7 (3.6)	3 (1.9)	4 (11.8)	**0.019**
Pericarditis, n = 193	9 (4.7)	7 (4.4)	2 (5.9)	0.66
Digestif ultrasound, n (%)				
Hydrocholecyst, n = 86	6 (7.0)	3 (4.7)	3 (13.6)	0.38
Therapeutics, n (%)				
Corticosteroids	18 (9.3)	7 (4.4)	11 (32.4)	**<0.001**
IVIG				0.08
1 g/kg	23 (11.9)	22 (13.8)	1 (2.9)	
2 g/kg	171 (88.1)	138 (86.2)	33 (97.1)	

Values in bold mean that the values are statistically significant.

Our study showed that low serum sodium was an independent factor associated with a high risk to develop resistant KD. The pathophysiology is poorly understood, but in the acute phase in KD, interleukin Il-6 and IL-1B are elevated. This process is related to antidiuretic hormone secretion leading to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and hyponatremia.[32] Low serum sodium levels reflect the progress of inflammation in patients with KD. Nakabayashi et al reported that CRP, percentage of neutrophils and incidence of CAA were higher, and the hemoglobin level and total protein were lower in the hyponatremia group of KD patients, which indicate the hyponatremia group having more severe inflammation.[33] Nakamura et al showed that sodium might be the most useful predictor of giant aneurysms caused in KD.[34]

TABLE 2. Univariate Logistic Regression Analysis of Resistant KD Predictors' Factors

Variables	OR and CI (95%)	*P*
Age of diagnostic < 12 months	2.05 (0.85–4.70)	0.096
Day of fever at diagnosis < 5 days	1.48 (0.68–3.43)	0.340
Changes in the extremities	1.89 (0.88–4.27)	0.110
Serum sodium < 133 mmol/L	2.97 (1.40–6.45)	**0.005**
Hemoglobin level < 110 g/L	3.17 (1.46–7.34)	**0.005**
Platelet count < 300 G/L	1.15 (0.50–2.50)	0.731
AST > 100 UI/L	1.06 (0.23–3.55)	0.929
Albumin level < 30 g/L	2.51 (0.99–7.26)	0.066
Neutrophils > 80%	2.36 (1.03–5.25)	**0.037**
CRP > 150 mg/L	4.47 (2.07–10.19)	**<0.001**
Coronary artery abnormality	3.85 (1.67–8.79)	**0.001**
Myocarditis	6.98 (1.47–36.95)	**0.014**
Pericarditis	1.36 (0.20–5.93)	0.711

CI, confidence interval.
Values in bold mean that the values are statistically significant.

We failed to set up a predictive score of resistant KD potentially because the resistant KD population was too small.

Our study has strengths. First, the accuracy of data collected: only 8 patients are nonincluded. This is a multicenter study, including 2 university hospitals, with all 5 of secondary hospitals of one of them so a completely and representative pediatric population of a region in Eastern France. In addition, our data collect has been exhaustive and we had little lack of data among those presented. Selection biases were limited: all KD patients need hospital care (probably almost all of them were identified). Second, it is only the second French study with the same objective—more research studies in France or in Europe are necessary. To finish, factors identified have similarities with different scores and the definition of resistant KD is based on recent practice guidelines.

TABLE 3. Multivariate Logistic Regression Analysis of Resistant KD Predictors' Factors

Variables	OR and CI (95%)	*P*
Hemoglobin level < 110 g/L	2.39 (0.96–5.98)	0.061
Serum sodium < 133 mmol/L	2.7 (1.12–6.48)	**0.026**
Albumin level < 30 g/L	2.48 (0.86–7.15)	0.093
CRP > 150 mg/L	2.29 (0.95–5.55)	0.065

Value in bold mean that the values are statistically significant.

There are some limitations too. First, the size of our sample was potentially too small to allow us to draw any conclusions regarding the link between some criteria and a resistant KD (eg, age < 12 months or albumin level). Second, it was a retrospective study, which still explains a lack of data, particularly about laboratory variables (AST 6% lack of data, albumin level 34%, PCT 40% and ESR 64%) and some data did retrospectively choose not to analyze (eg, lipasemia [n = 28], ferritin count [n = 34] and BNP [n = 16]).

In conclusion, this study shows an association between resistant KD and biologic and echocardiography criteria in an Eastern French region, but only serum sodium is an independent predictive factor. A future study may include more centers, to increase the number of resistant KD and to set up a predictive score and/or test the one recently established by a French team.

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