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ORIGINAL ARTICLE

MULTISYSTEM INFLAMMATORY DISORDER IN CHILDREN AND KAWASAKI DISEASE IN THE COURSE OF THE SARS-COV-2 PANDEMIC

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ABSTRACT

After the onset of the new SARS-CoV-2 coronavirus pandemic, several countries reported an increase in cases of Kawasaki Disease (KD) in the pediatric centers. KD, also called mucocutaneous lymph node syndrome, presents as an acute, multisystem pediatric vasculitis of unknown etiology. In this present study, we research to determine the influence of SARS-CoV-2 on the manifestation of KD, the overlap with the so-called Multisystem Inflammatory Syndrome in children (MIS-C) and to compare the main characteristics of these pathologies, since this relationship was evidenced throughout the year of 2020 with pediatric patients infected with coronavirus. To carry out the work, it was performed a systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses - PRISMA. Articles published or pre-published in the PubMed and Scielo databases in 2020 were considered. A total of 924 scientific articles were identified, and after excluding duplicates from the selection and data extraction, 52 remained for data comparison. None of the analyzed parameters, such as clinical manifestation, age of affected patients, laboratory variants showed a significant difference between the two groups, associated with the fact that there was no increase in the number of KD cases in the absence of concomitant SARS-CoV-2 infection, compared to pre-pandemic period. Thus, we conclude that MIS-C and KD concomitant with Coronavirus Disease 2019 (COVID-19) were named without technical criteria given the urgency in publishing information during the period of severity of the COVID-19 pandemic.

KEY WORDS: COVID-19; SARS-CoV-2; Kawasaki Disease; Multisystem I nflammatory Syndrome in children.

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INTRODUCTION

The first case of Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) virus was reported by the World Health Organization (WHO) on December 31, 2019, due to emergence of cases of a pneumonia-like illness with no known etiology in Wuhan City, China. Late January of 2020, the WHO Emergency Committee announced a global health emergency in light of the increasing rate of cases in the Chinese region as well as internationally (WHO, 2020).

After the onset of the new coronavirus pandemic, several countries reported an increase in cases of Kawasaki Disease (KD) in their pediatric centers. A medical report from the province of Bergamo, Italy, highlighted a 30-fold increase in KD cases in the period from February to April 2020, compared to the last five years (Verdoni et al., 2020).

The first case report was published in early April 2020 (Jones et al., 2020), but the first big warning was on April 26, when the National Health Service of the United Kingdom (NHS UK) issued a note to highlight an increase in cases of critically ill children with overlapping features of toxic shock syndrome, atypical KD and concomitant COVID-19 infection (PICS, 2020).

Later, it was reported by the Royal College of Pediatrics and Child Health (RCPCH), the US Centers for Disease Control and Prevention (CDC) and the World Health Organization. Several terminologies have been used to describe this condition, such as Kawasaki-Like Syndrome (KLS), atypical KD, incomplete KD, Kawa-COVID-19, and hyper inflammatory syndrome Kawasaki type induced by SARS-CoV-2 (Licciardi et al., 2020).

The US CDC called this presentation MIS-C (Multisystem Inflammatory Syndrome in Children), the World Health Organization used similar terminology and added adolescents (Multisystem Inflammatory Syndrome in Children and Adolescents), and the Royal College of Pediatrics and Child Health used the terminology Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). The parameters used to designate this condition differ slightly between the three Institutions, however, common characteristics to all include the presence of fever, hyper-inflammatory state and organ dysfunction (Kabeerdoss et al., 2021).

The KD presents as an acute and multisystem pediatric vasculitis of unknown etiology, first recorded in 1967 by pediatric physician Dr. Tomisaku Kawasaki. Its incidence peaks in children from the age of six months to five years old and its risk is 1.5 higher in boys than in girls (Kawasaki, 1967).

Diagnosis of KD is based on criteria outlined in the 2017 guidelines issued by the American Heart Association. Patients who meet the case definition are considered to have complete KD or classic KD, while those who do not have sufficient major clinical findings may be diagnosed with incomplete or atypical KD. Diagnosis of classic KD is based on fever for five or more days,

together with at least four of the five main clinical features: (a) oral changes including erythema, chapped lips, 'strawberry tongue' and diffuse erythema of the oropharyngeal mucosa, (b) bilateral bulbar conjunctival infection, (c) erythematous eruption, (d) erythema and edema of the hands and feet, and (e) cervical lymphadenopathy at least 1.5 cm in diameter. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases (McCrindle et al., 2017).

Several worldwide reports on the natural course of MIS-C and its epidemiology were published after the initial reports from Europe of MIS-C and many of these studies compared MIS-C with severe COVID-19 shock and KD (Bassareo et al., 2020; Bordet et al., 2020; Verdoni et al., 2020).

In this systematic review, we research to determine the influence of SARS-CoV-2 on the manifestation of KD, the overlap with the so-called Pediatric Multisystem Inflammatory Syndrome and compare the main characteristics of these pathologies. Since this relationship was evidenced during the year 2020 in pediatric patients infected with coronavirus, the concomitant increase in the number of cases with signs and symptoms similar to those of KD. The aim of this review was to describe the frequencies of clinical characteristics of pediatric patients diagnosed with KD or MIS-C and COVID19-positive in order to answer to the question: what is the current situation regarding KD during the pandemic, in particular its relationship with MIS-C?

MATERIAL AND METHODS

The review was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses - PRISMA. Articles published or pre-published from January 2020 to December 2022 were considered. The methodology that guided the review was Population/ patient, Exposition, Control and Outcomes (PECO). According to these criteria: P, children who developed MIS-C or KD; E, exposition was the SARS-CoV-2; C, control was not applied; O, clinical manifestations of both MIS-C and KD associated to COVID-19 positive.

Research strategy

The research for scientific articles was performed in the Public Medline (PubMed), Scientific Electronic Library Online (Scielo), Scopus, Web of Science, Europe PMC, and Embase databases. The descriptors used for the search were "Kawasaki disease AND COVID-19", "Kawasaki disease AND SARS-COV-2", "Multisystem inflammatory syndrome AND COVID-19", "Multisystem inflammatory syndrome AND SARS-COV-2".

Eligibility Criteria

Records were included if they examined the clinical features of patients diagnosed as KD or MIS-C being positive for COVID-19. Primary outcomes of interest included key clinical events concern both conditions after SARS-CoV-2 infection.

All primary study design included case reports, case-control studies, cohort studies and observational studies published or pre-published that positively identified children defined with age less than 18 years old with potential diagnosis of MIS-C in addition to a positive SARS-CoV-2 PCR test result or SARS-CoV-2 serum antibody assay. There were linguistic restrictions, and only articles in English, Portuguese or Spanish were included. There were no restrictions regarding the country of articles production. Only reports published or accepted after January 2020 were eligible, as MIS-C or KD prior to this date is not related to SARS-CoV-2. Letters to the editor, literature reviews, systematic reviews, meta-analyses, abstracts, articles without COVID testing and without clinical data were not included in the study design. In addition, analysis in patients with any systemic disease was not considered.

Study Selection

In accordance with the research strategy established above, all retrieved studies were independently selected by two reviewers after the elimination of duplicates. Any discrepancies were resolved by discussion, consulting a third reviewer when necessary. First, titles and abstracts were selected to exclude irrelevant studies. Second, potentially eligible studies were evaluated by reviewing the full texts to ensure that they all meet the inclusion criteria. All reasons for excluding ineligible studies were recorded, and the study selection process was documented using a PRISMA flowchart (Figure).

Data Extraction

The clinical variables collected in the data extraction were: sex, age, clinical symptoms related to KD or MIS-C, heart problems, respiratory problems, gastrointestinal problems and test results for the COVID-19. As for the laboratory variables collected, they were white cell count, C-reactive protein, ferritin and platelet count.

Quality assessment

Independently, the same reviewers assessed the methodological quality of the selected studies according to their level of evidence, as proposed by the Joanna Briggs Institute. Methodological Index (Slim et al., 2003) with some adjustment. Discrepancies between the reviewers were also discussed. In the final analysis, based on assessment questions, studies were categorized as "high quality" when the study achieved over 7 points, "moderate quality" when the study reached 5-7 points, and "low quality" when the study reached up to 4 points, for a total score of 10 (Table 1).

RESULTS

A total of 927 potentially relevant references were identified in the search, 508 were considered duplicated and they were therefore removed. After titles and abstracts screening, 298 studies remained. Reading the complete texts resulted in exclusion of 75 more studies due to: study design as letter to the editor, literature reviews, systematic reviews, or meta-analyses; because they did not evaluate report, or they have the clinical manifestations; due to patients being older than 18 years old; no COVID-19 test. Overall, 46 studies were selected for the analysis (Table 1). Details of the research strategy are presented in Figure.

The period of publication of the articles included in the study was between June, 2020 and December, 2021. The articles were from Brazil, England, France, Germany, India, Iran, Israel, Italy, Norway, Pakistan, Poland, Portugal, Saudi Arabia, Serbia, Spain, Turkey, and the United States. Of the 46 articles analyzed, 34 were case reports and 12 presented a series. In total, 118 cases of KD/MIS-C were included in the present study, with 31 cases named by the authors as KD and 87 cases named as MIS-C.

The ratio between male and female was approximately 1.8:1.0 in both the KD and MIS- C groups and the predominant age was between 10 and 15 years old, also for both groups (Table 1).

Regarding the clinical characterization of the analyzed cases, we did not observe any significant discrepancy between the KD group and the MIS-C group for most of the investigated signs/ symptoms. Only for gastrointestinal symptoms, including diarrhea, vomiting and abdominal pain, the frequency was much higher in the MIS-C group.

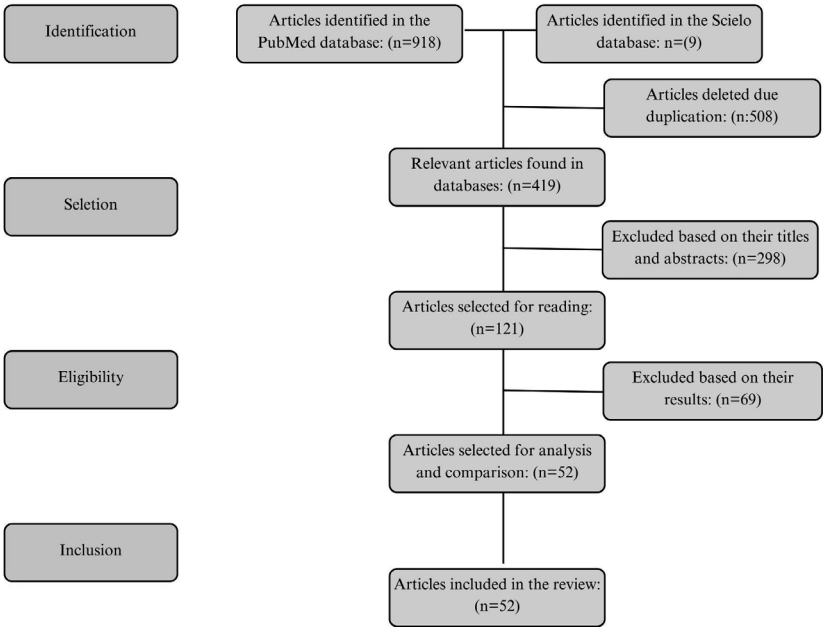

Figure. PRISMA flowchart on the search strategies in the databases until the final inclusion of records.

Respiratory symptoms were slightly more frequent in the MIS-C group, but not expressive. The cardiovascular symptoms observed in both groups also did not show any discrepancy between them. Overall, cardiovascular symptoms were slightly more frequent in the MIS-C group, whereas myocarditis was more frequent in the KD group (Table 2). As for the KD criteria, we did not observe significant difference between the frequencies of these signs in the KD and MIS-C groups. Only conjunctivitis was more frequent in the MIS-C group and edema, erythema of hands and feet was more frequent in the KD group (Table 1).

Laboratory findings (Table 2) were: leukocytosis, increased C-reactive protein, normal platelet count and increased ferritin. These variables were evaluated in complete KD, incomplete KD and MIS-C, and it did not detect any difference between these variables in the two groups.

Table 1. Clinical characterization of the cases included in this study. KD: Kawasaki Disease. MIS-C: Multisystem Inflammatory Syndrome in Children.

Cases Clinical Characterization	Frequency		
		KD	MIS-C
Age (years)	0-5	9/31 (29.0%)	14/87 (16.5%)
	5-10	9/31 (29.0%)	33/87 (38.2%)
	10-15	13/31 (42.0%)	37/87 (45.2%)
Sex	Male	19/31 (63.0%)	57/87 (66.0%)
	Female	11/31 (36.8%)	29/87 (34%)
Fever		31/31 (100%)	87/87 (100%)
Gastrointestinal symptoms	Abdominal pain	6/31 (21.0%)	62/87 (71.3%)
	Vomit	4/31 (13.0%)	49/87 (56.5%)
	Diarrhea	9/31 (31.5%)	54/87 (62.6%)
Respiratory symptoms		9/31 (29.0%)	38/87 (43.4%)
Cardiovascular symptoms	Tachycardia	11/31 (36.8%)	33/87 (38.2%)
	Hypotension	11/31 (36.8%)	38/87 (43.4%)
	Coronary artery aneurysm/ ectasia	5/31 (15.7%)	22/87 (26.0%)
	Reduced ejection fraction	3/31 (10.5%)	16/87 (18.2%)
	Mitral regurgitation	4/31 (13.0%)	15/87 (17.3%)
	Pericardial effusion	3/31 (10.5%)	19/87 (22.6%)
	Myocarditis	7/31 (23.6%)	12/87 (14.0%)
	Left ventricular dilation	1/31 (3.2%)	5/87 (6.0%)
	Systolic and diastolic dysfunction	2/31 (7.8%)	7/87 (7.8%)
Kawasaki Disease Presentation	Complete	14/31 (47.3%)	-
	Incomplete	16/31 (52.6%)	-
Kawasaki Disease Criteria	1.Oral changes		
	Erythema	8/31 (26.3%)	10/87 (12.1%)
	Cracked lip	4/31 (13.1%)	7/87 (7.8%)
	"Strawberry tongue"	2/31 (7.9%)	4/87 (4.3%)
	2. Conjunctival infection	18/31 (57.8%)	45/87 (52.1%)
	3. Erythematous eruption	16/31 (52.6%)	53/87 (61.7%)
	4. Erythema and edema of the hands and feet	10/31 (34.1%)	5/87 (6.0%)
	5. Cervical lymphadenopathy	14/31 (47.3%)	7/87 (7.8%)
Total number of cases		118	
COVID-19 Test	PCR +	21/118 (17.8%)	
	Serologic +	97/118 (82.2%)	

Table 2. Laboratory findings in the two groups in the Kawasaki Disease (KD) and in Multisystem Inflammatory Syndrome in Children (MIS-C).

Criteria Investigated (reference values)	Laboratory findings	
	KD	MIS-C
White cell count ($\times 10^9$/L) (4.2 a 11,0)	10,8 - 14,0	3,54 - 8,1
C-reactive protein (mg/L) (0 a 10)	90 - 480	147 - 450
Platelet count ($\times 10^9$/L) (150 a 400)	66 - 275	42 - 336
Ferritin (ng/ml) (13.7 a 78)	199 - 3213	217 - 4387

DISCUSSION

It is controversial whether SARS-CoV-2 infection leads to KD or whether the symptoms refer to an overlap of what has been named Multisystem Inflammatory Syndrome present in children and adolescents who tested positive for Covid-19. In this systematic review, we sought to assess the emergence of KD cases and the relationship with cases designated as MIS-C in the face of the SARS-CoV-2 pandemic in individuals who are positive for COVID-19.

In this present study, 153 cases reported by the authors as KD or MIS-C, positive for COVID-19, were analyzed. Among them, 38 were diagnosed as KD and 115 as MIS-C. When comparing signs and symptoms between the two groups, no significant data was observed. The prevalence of males was observed in both groups with a male to female ratio of 1.5 to 1.0. The ratio between male/ female in KD is 1.5 to 1.0 (Tacke et al., 2014), whereas in MIS-C there is no defined ratio and, although there are more men diagnosed than women, this difference is not significant (Kabeerdoss et al., 2020). Cherqaoui et al (2021) found a male to female ratio of 1.4 in a group of individuals with MIS-C. Thus, the data collected in this study are in accordance with those described in the literature.

Regarding age, we observed a predominance of cases in the age from 10 and 15 years old, both for KD and MIS-C. The development of KD is age-specific, with children from six months to five years old at higher risk (McCrindle et al., 2017) which suggests a protective maternal passive immunity against the causative agent, from birth to six months of age, and the importance of maturation of the immune system in children $\geq$ 6 years of age

(Rowley, 2018). Among the 38 cases diagnosed as KD analyzed in this study, 70% the children were older than 5 years of age, and 42% were between 10-15 years old. These data indicate that in cases of KD concomitant with COVID-19 there was a discrepancy regarding the expected age of onset of the disease. In MIS-C, a predominance of cases older than five years is observed, with the mean age of some cohorts reported as 8.3 years old (Cattalini et al., 2021; Cherquaoui et al., 2021), which was also observed in the present analysis, where 83% of the cases were aged ≥ 5 years old.

Gastrointestinal manifestations have been reported in 70% of patients with MIS-C and the clinical presentation mimics viral gastroenteritis or inflammatory bowel disease with nausea, vomiting, diarrhea and abdominal pain (Kaushik et al., 2020). These data were corroborated in this present analysis, where we observed that 71.3% of the cases had abdominal pain, followed by diarrhea (62.6%) and vomiting (56.5%). In the KD group, this frequency was approximately 30%, revealing a clear discrepancy between the groups. Studies have reported that the frequency of gastrointestinal manifestations in patients with KD concomitant with COVID-19 is higher when compared to patients with KD only (Cattalini et al., 2021). However, there are no data comparing the frequency of these manifestations in patients with KD and MIS-C both positive for COVID-19. This finding may be random or indicate that some authors focused only on the KD classification criteria and it did not report other symptoms that could be present in the cases.

Among the 153 cases analyzed, 105 (68.6%) had cardiovascular manifestations. There was no significant difference between the frequencies of the types of cardiac manifestations in the two groups. Coronary artery aneurysm and pericardial effusion were more frequent in the MIS-C group, while myocarditis was more frequent in the KD group, although there was no significant difference between these frequencies in the analyzed groups.

KD is an acute vasculitis and approximately 25% of those who are not treated develop coronary artery aneurysms. In the developed world, it has surpassed rheumatic fever as the most common cause of acquired heart disease (McCrindle et al., 2017). Cardiac anomalies in the acute phase of KD can include tachycardia, myocarditis, congestive heart failure, pericardial effusion, and mitral regurgitation. These cardiac manifestations are also reported in patients diagnosed as MIS-C (Yashuara et al., 2020). Thus, these symptoms are not able to distinguish between the two pathologies, as shown by the results of this analysis, since there was no difference between the frequencies of these manifestations and, furthermore, coronary artery aneurysm was slightly more frequent in the MIS-C than in KD.

Regarding the criteria used for the diagnosis of KD, the ones that were more frequent were erythema/ edema of feet and hands and cervical lymphadenopathy when compared to cases described as MIS-C. The other characteristics were presented at similar frequencies in the two analyzed groups, not standing out as distinguishers between KD and MIS-C.

Patients in the acute phase of KD usually have neutrophil-predominant leukocytosis. Elevation of acute phase reagents such as erythrocyte sedimentation rate (ESR) and C-reactive protein is always present and it is considered a key criterion, particularly in cases of incomplete KD (MacCrindle et al., 2017). The majority of MIS-C patients appear to have a hyperinflammatory state manifesting as neutrophilic leukocytosis, increased erythrocyte sedimentation rates, hyponatremia, hypertriglyceridemia, elevated C-reactive protein levels, procalcitonin, d-dimer, and serum ferritin. MIS-C patients generally have lower platelet counts and higher ferritin levels compared to KD patients. MIC children have lower leukocyte (white cell) counts compared to patients with KD and healthy children (Consiglio et al., 2020). In the present systematic review, the laboratory findings related to the dosage of C-reactive protein, ferritin, white cell and platelet counts in the KD and MIS-C groups did not indicate any significant difference between them, whose mean measured dosages were practically the same in both groups. Thus, this was also an item that did not show to be different between the groups, indicating that individuals classified as KD, positive for COVID-19, have the same laboratory parameters as individuals classified as MIS-C. Authors who support the connection between KD and MIS-C argue that the difference in laboratory values observed when comparing some studies can be partly explained by the different genetic compositions of the cohorts with which they were compared (Whittaker et al., 2020).

Most of the cases evaluated in the present study had a positive diagnosis for COVID-19 by the serological test (63%), and many of them, initially, had a negative RT-PCR test. This result corroborates with others published and indicates that many of these cases occurred after several weeks of quarantine, and it is possible that these individuals suffered from a mild form of COVID-19 after intrafamilial transmission and serious complications emerged weeks later, probably related to a response dysregulated immune system. The temporal relationship between the infection curves and the reported cases would also be consistent with this hypothesis (Koné-Paut & Cimaz, 2020).

For many authors who argue that KD and MIS-C are etiologically different entities, the arguments are that MIS-C individuals have a higher age of presentation, a deeper form of inflammation than KD or KD shock syndrome, more gastrointestinal manifestation, different laboratory findings including lymphopenia, thrombocytopenia, elevated troponin, elevated NT-proBNP, elevated D-dimer and elevated ferritin and they have a greater propensity for LV dysfunction and shock compared to patients with KD (Whittaker et al., 2020). The data found in this review do not show differences in any of the items

mentioned, which indicates that in the individual positive for COVID-19, the manifestations classified as KD are the same or, in a certain way, they overlap with the clinic classified as MIS-C.

In contrast to classic KD, pediatric systemic inflammation after SARS-CoV-2 infection affects older children and adolescents. Another observation is that patients with severe forms are less commonly Caucasian than expected in their general population, revealing many of African-American or African-Caribbean ethnicity. Furthermore, these cases have not been reported in Korea and Japan where there are the highest incidences of KD and SARS-CoV-2 was present in these areas as well.

Regarding clinical characteristics, most cases reported do not meet the definition of the American Heart Association criteria for KD or, in a minority of cases, present only incomplete forms of KD (Koné-Paut & Cimaz, 2020). Therefore, the distinct etiological entity with distinct parameters refers to the individual diagnosed with KD, negative for COVID-19 when compared to the individual diagnosed as MIS-C and, of course, positive for COVID-19. Some studies indicate that despite some similarities, there is epidemiological, clinical and laboratory evidence supporting the concept of a new syndrome separate from KD and this semantic distinction is very important, since the name Kawasaki has generated confusion in the media, patients and families that suffered with this condition in the past raised doubts and uncertainties (Koné-Paut & Cimaz, 2020).

It is clear that during the health crisis caused by COVID-19, all information was welcome and the rigor in the evaluation of scientific articles was relaxed so that the information was made available in a short period of time. Thus, there was no time to standardize a term, a concept or a better definition on the presentation of clinical manifestations in the course of the SARS-CoV-2 pandemic involving KD. With the result of the present work, where all cases were positive for COVID-19, we observed that some studies called the clinical presentation simply as KD while others called it as MIS- C, during the year 2020. In 2021, the studies were more cautious in their denominations, and observations between distinctions regarding KD and MIS-C were pointed out (Cattalini et al., 2021), especially in the absence of SARS-CoV-2 infection.

Then, with the data obtained in this systematic review, where none of the analyzed parameters showed a significant difference between the two groups, associated with the fact that there was no increase in the number of KD cases in the absence of concomitant SARS-CoV-2 infection, in comparison to periods prior to the pandemic, we concluded that MIS-C and KD concomitant with COVID-19 reported during 2020 were named without a technical rigor for their definition given the urgency in the disclosure of information. Long-term studies with individuals with MIS-C concomitant with COVID-19, in the form of data recording and genomics, may help to define the clinical course, epidemiology, mechanism of MIS-C, and even KD itself.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest to disclose.

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