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(i)**Original research article**

(ii) Multicentre observational study on multisystem inflammatory syndrome related to COVID-19 in Argentina

(iii) Running title: Multicentre study on SIM-C in Argentina

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ABSTRACT

BACKGROUND

The impact of the Pediatric Inflammatory Multisystem Syndrome temporally-associated with SARS-CoV-2 (PIMS-TS) in low and middle-income countries remains poorly understood. Our aim was to understand the characteristics and outcomes of PIMS-TS in Argentina.

METHODS

This observational, prospective and retrospective multicenter study, enrolled patients younger than 18 years-old showing PIMS-TS, Kawasaki disease (KD) or Kawasaki shock syndrome (KSS) manifestations between March 2020 and May 2021. Patients were followed-up until hospital discharge or death (which occurred in one case). The primary outcome was PICU admission. Multiple logistic regression was used to identify variables predicting PICU admission.

RESULTS

Eighty-one percent, 82% and 14% of the 176 enrolled patients fulfilled the suspect case criteria for PIMS-TS, KD, and KSS, respectively. Temporal association with SARS-CoV-2 was confirmed in 85% of the patients and 38% were admitted to PICU. The more common clinical manifestations were fever, abdominal pain, rash and conjunctival injection. Lymphopenia was more common among PICU-admitted patients (87% versus 51%, $p<0.0001$), who also showed a lower platelet count and higher plasmatic levels of inflammatory and cardiac markers. Mitral valve insufficiency, left ventricular wall motion alterations, pericardial effusion and coronary arteries alterations were observed in 30%, 30%, 19.8%, 18.6% of the patients, respectively. Days to initiation of treatment, rash, lymphopenia, and low platelet count did significant independent contributions to PICU admission.

CONCLUSION

Rates of severe outcomes of PIMS-TS in the present study agreed with those observed in high-income countries. Together with other published studies, this work helps to better understand this novel clinical entity.

Key words SARS-CoV-2, Kawasaki Disease, Pediatric Multisystem Inflammatory Syndrome (PIMS), Multisystem inflammatory syndrome in children, COVID-19, Kawasaki Shock Syndrome.

Introduction

Since the beginning of the SARS-CoV-2 pandemic more than 9 million cases and 280 deaths per 100000 population have been recorded in Argentina. Children less than 10 years old accounted for 2.5% of the cases and 0.15% of the deaths (1). A multicenter study carried out between April 2020 and May 2021 based on 2960 confirmed pediatric cases reported a median age of 5.6 years and mild or no symptoms in over 90% of the cases (2). However, as it happened in Europe and the United States, a few weeks after detection of the first adult case, children's hospitals began to receive an unusually elevated number of patients showing multisystem inflammatory syndrome (3–9). This syndrome shares clinical manifestations with Kawasaki disease (KD), Kawasaki Shock Syndrome (KSS), and Macrophage Activation Syndrome (MAS). The condition is now known as Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV2 (PIMS-TS) or Multisystem Inflammatory Syndrome associated with Coronavirus Disease (MIS-C) (10,11). The Argentine Ministry of Health posted a suspected case definition in July 2020 (1).

Although severe illness due to SARS-CoV2 infection is uncommon in children, PIMS-TS can lead to hospitalization and severe outcomes. Also, its long term effects on health are yet to be determined and the impact of PIMS-TS in low and middle income countries (LMICs) remains poorly understood. The high mortality rates due to SARS-CoV-2 pandemic in Latin America have been related to the pervasive financial difficulties, poverty, social inequalities and health system fragility affecting the region (12), raising concern about PIMS-TS outcomes. Therefore, the "Dr. R. Gutierrez" and "Dr. J. Garrahan" Children Hospitals, -centers of reference for patients with KD and related conditions-, organized the present observational multicenter study. The study aimed to characterize patients with KD-like multisystemic disease during the SARS-CoV-2 epidemic by evaluating clinical manifestations, laboratory data, echocardiogram alterations, outcome, and relationship with virus outbreak, with emphasis on predicting risk of severe illness requiring PICU admission. In addition, since there was a high prevalence of echocardiogram alterations, the patients were re-evaluated within two months after discharge from hospital to determine if there were any persisting abnormalities.

Methods

Patients and study design

This observational, prospective and retrospective, multicenter study enrolled 176 patients aged up to 18 years old showing PIMS-TS/KD symptoms that were admitted to 14 hospitals in Argentina, mostly from the City of Buenos Aires and its surrounding areas (Metropolitan Buenos Aires Area), between March 2020 and May 2021. Thirty-five of the patients were enrolled retrospectively. The inclusion criteria were: cases fulfilling diagnostic criteria for KD (13), KSS (14) or PIMS-TS (15,16), with or without a positive SARS-CoV-2 test or close contact in its recent medical history. Patients having an acute SARS-CoV-2 infection without clinical criteria for KD or PIMS-TS were not included. All patients had SARS-CoV-2 antigen and/or PCR tests and those

testing negative (n=31) were preserved in the study even if they were not close contacts of SARS-CoV-2 positive cases. Patients were followed up until hospital discharge or death (which occurred only in one case). Instructions for reporting case characteristics were distributed and then collected by email. Collected data were added to a central Excel database. Cases were tagged with numbers indicating the order of enrollment to de-identify the data. Informed consent forms and study procedures were approved by each hospital review board. There were no interventions as part of this study.

Collected data

Patients' demographics, age, sex, weight, comorbidities, clinical manifestations, time from symptom onset to diagnosis, hospital admission, and initiation of treatment, duration of admission, days at PICU, days of mechanical ventilation, and laboratory, electrocardiographic and echocardiographic data, were collected during the acute phase of the illness (first 12 days). Some data could be collected again 13 to 60 days after the beginning of symptoms. Patients were assessed by trained clinicians and classified as having PIMS-TS based on the fulfillment of WHO and Argentine Ministry of Health diagnostic criteria (15,16), typical, atypical or incomplete forms of KD according to American Heart Association guidelines (13), KSS following the study of Kanegaye et al. (14) and MAS according to classification criteria described in Ravelli et al. (17). Acute myocardial alterations were defined according to the American Heart Association criteria (13). Each patient could fulfill criteria for many of the conditions.

Outcomes

The primary outcome measure was PICU admission. Additional exploratory outcomes were myocardial involvement, shock/severe hypotension, and mechanical ventilation requirement.

Statistical analysis

Two investigators (SB and MGM) screened the database for errors related to standardization of variables in each hospital, sent queries to investigators at each center and corrected the database when necessary. Cases with missing data were not imputed. Data are reported as number of observations and percentages, or medians and IQRs, for categorical and continuous variables respectively. Between group differences were assessed with Fisher's exact test (FET), chi square test, Mann Whitney U test or Kruskal Wallis test as appropriate. For some normally distributed variables, the data are presented as mean and SEM, and between group comparisons were performed using the Student´s t test. All tests were two-sided and a p value of <0.05 was considered to be statistically significant. Pearson correlation matrices were used to explore relationships between variables.

To identify independent predictors of PICU admission, variables with a p value <0.05 differing between admitted and non-admitted patients were selected. Special care was taken to avoid redundancy based on the analysis of correlation matrices and to minimize loss of cases by missing data. These variables were submitted to a multiple logistic regression analysis using Akaike

information criterion and a stepwise procedure to choose the model that best fits the data (18). Age, weight, duration of admission and symptoms, and laboratory data were introduced as continuous variables. Sex, clinical manifestations, comorbidities, and SARS-CoV-2 test results were entered as categorical variables. The model significance was established using the likelihood ratio test procedure. Adjusted risks were expressed as odd ratios (OR) with 95% confidence intervals [CI95%]. A Receiver Operating Characteristic (ROC) curve was built to study the classification power of the model.

Statistical analyses were performed with R studio and Graphpad 9.0

Funding

There was no specific funding source for this study. The corresponding author had full access to all the data and analysis had final responsibility for the decision to submit for publication.

Results

Data on 176 patients fulfilling the case definition for KD, KSS and/or PIMS-TS were included in the database. The median age was 72 months (range, 1 to 191 months) and 104 patients (59%) were male (Table 1). Sixteen percent of the patients had comorbidities (number of patients with comorbidities: obesity, 6; renal disease, 5; neurologic, oncohematologic, respiratory and genetic diseases, 3 patients each; some patients presented more than one). Patients lived in Buenos Aires City and its surroundings (78%), and in Mendoza Province (22%). The first case was reported on March 23th, 2020, twenty days after detection of the first adult case, and the enrolment rate was highest during the first wave peak that took place in the spring (September and October, 2020; Figure 1). One hundred and thirty nine patients had a positive SARS-CoV-2 test and ten patients with negative test results but that fulfilled criteria for close contact were also considered temporally-associated with SARS-CoV-2 (Table 1). Among the 176 patients, 81.2%, 81.8%, 14% and 1.1% fulfilled the suspect case criteria for PIMS-TS, KD, KSS and MAS respectively. Thirty eight percent of the patients (67/176) were admitted to PICU for a median of 5.5 days (IQR: 3 to 9 days), and did not differ from non-admitted patients in sex, weight, age or presence of comorbidities. Among them, 43% required mechanical ventilation, 67% had shock or severe hypotension requiring inotropic support, and one patient died. Patients classified as PIMS-TS and showing an atypical KD presentation were more represented in the PICU admitted group. Moreover, a higher proportion of positive SARS-CoV-2 serologic test patients was observed in the PICU admitted group. Finally, PICU admitted patients remained in the hospital for longer (7 versus 12 days, $p<0.0001$) and required treatment sooner (median: 4 versus 6 days, $p<0.0001$) than non-admitted patients (Table 1). Less than 5 years old patients stayed more days at the hospital than older patients (Table S1).

The more common clinical manifestations were fever, abdominal pain and/or diarrhea, rash, conjunctival injection, and oral mucous membrane changes (Table 1). There were not marked differences in the patients admitted to PICU, which showed more commonly abdominal pain/diarrhea and pneumonia/pneumonitis, and less frequently rash and BCG reactivation, than

non-admitted patients. The lower proportion of rash in PICU admitted patients is limited to less than 5 years old patients, who also had jaundice more frequently, while the higher proportion of abdominal pain/diarrhea is only seen in patients older than 5 years old (Table S1). Six patients showed fever and coronary artery echocardiography alterations as sole clinical manifestation; five of them required PICU admission. Other less common clinical manifestations whose frequency did not differ between PICU admitted and non-admitted patients were irritability (19% of patients), urethritis (16%), confusion (15%), Beau's lines (9.1%), jaundice (4.5%), BCG reactivation (3.4%) and arthritis (3.4%). Acute abdomen (7.4%), acute renal failure (4.5%), seizures (2.3%) and aseptic meningitis (1.1%) were observed in a minority of the patients.

Lymphopenia was very common affecting 65% of all patients, and was more common among patients admitted to PICU than in non-admitted patients (87% versus 51%, $p<0.0001$; Table 1). Lymphopenia was particularly common in PICU admitted >5 years old patients (44/46 patients), which had a median lymphocyte cell count of 810 lymphocytes/µl (IQR: 568-1092 lymphocytes/µl) (Table 1S). Patients admitted to PICU showed a lower platelet count and higher plasmatic levels of inflammatory (C-reactive protein, procalcitonin, and ferritin), and cardiac markers (ten-fold increase of pro-brain natriuretic peptide and five-fold increase of troponin), than non-admitted patients (Table 1). In addition, 32% of all patients showed elevated plasmatic transaminase levels without differences between PICU admitted and non-admitted patients. Yet, PICU admitted patients had higher plasmatic levels of bilirubin and lower levels of plasmatic albumin (Table 1). The changes in transaminases and bilirubin were more marked in less than 5-year-old patients (Table S1).

Forty eight percent of the patients showed acute cardiac alterations. The more frequent ECG alterations were sinus tachycardia (31%), repolarization alterations (15%), and conduction blocks (5.7%) (Table 1). The echocardiogram showed alterations in 49.4% of the patients including coronary arteries alterations in 32 of 172 patients (Table 1). The most common alterations were mitral valve insufficiency (30%), pericardial effusion (19.8%), and tricuspid valve insufficiency (17%). These changes were more frequently observed in patients admitted to PICU (Table 1), who also frequently showed left ventricular wall motion alterations (30%), ventricular dilatation (18%), and a significantly smaller fractional shortening (median: 32%, IQR: 28.5-36.5) than patients not requiring PICU admission (median: 38%, IQR: 35-42.6). The more common coronary artery alterations were increased refringency (32 reports), and mild to moderate dilatation (29 reports) affecting the right (23/32 patients), left (20/32 cases), and anterior descending (9/32 cases) coronary arteries. There were no differences between older and younger patients (Table S1).

Patients tagged as having acute myocardial alterations are compared to patients not showing markers of acute myocardial alterations in Table 2. There were no significant differences of age, sex or temporal association with SARS-CoV-2 infection, nor in the clinical manifestations, except for a more frequent presence of conjunctival injection and oral mucous membrane changes in patients with acute myocardial involvement. Patients with myocardial alterations required PICU

admission (62% versus 16%, p<0.0001) and mechanical ventilation (27.4% versus 6.3%) more frequently than patients without it, and showed shock/severe hypotension more commonly (43 versus 16% of the cases, p<0.0001). They showed increased levels of inflammatory and cardiac markers, and significantly smaller platelet and lymphocyte cell counts. Yet, the proportion of patients with lymphopenia (72% versus 59%), coronary artery alterations (22% versus 15%), and albumin plasmatic levels changes (median: 3.2, IQR: 2.7-3.6 g/dl; median: 2.9, IQR: 2.5-3.5 g/dl) did not differ in patients with and without acute myocardial alterations. As expected, most ECG and echocardiogram parameters were more altered in patients with acute myocardial alteration including reduced MAPSE and fractional shortening (Table 2).

We noticed that shock/severe hypotension was related to PICU admission, yet, 21 out of 67 of patients did not show shock/hypotension. The patients showing shock/severe hypotension stayed more days at PICU and required mechanical ventilation more frequently than no shock patients. In addition, they showed a more marked decrease of plasmatic proteins including albumin (Table S2). However, there were not any significant differences in the echocardiogram findings between the two groups of PICU admitted patients, including fractional shortening, which was low in both groups (Table S2). Interestingly, only 24 of the 46 patients with shock/severe hypotension fulfilled the diagnostic criteria for KSS. In the KSS patients, the male/female ratio was 0.60 (9/15) whereas in the no-KSS group this ratio was 2.14 (15/7; FET: p=0.0454), suggesting that the KSS diagnosis identified a singular group of patients. Furthermore, the shock no-KSS patients showed less frequently conjunctival injection (8/22 versus 18/24, FET: p=0.0163) and oral mucous membrane changes (4/22 versus 15/24, FET: p=0.0031) than KSS patients.

To better understand the relationship of some of the recorded variables with the chances of PICU admission (as an index of disease aggravation), we built a multivariate logistic model (see Methods). We studied the following variables: age, sex, weight, pre-existing conditions, days from first symptoms to initiation of treatment or diagnosis, rash, lymphopenia, platelet count, and temporal association with SARS-CoV-2 infection. Rash, lymphopenia, and platelet count were selected because they showed large significant differences between admitted and non-admitted patients (Table 1), and the data were available for most of the cases. After eliminating patients with missing data, 152 cases could be used for logistic regression analysis. Stepwise selection of variables ruled out any contribution of sex, weight, and pre-existing conditions, and showed a marginal contribution of age and temporal association with SARS-CoV-2 infection (p between 0.05 and 0.15 in at least one of the models tested during iteration). Days to initiation of treatment, fever days to diagnosis, rash, lymphopenia, and thrombocytopenia did a significant independent contribution to the outcome (Table 3; Figure 2A). Earlier need of hospitalization was associated with a higher probability of PICU admission. Twenty six percent of the patients that had symptoms for at least 7 days were admitted to PICU, contrasting with 63% and 91% of those that had symptoms for up to 4 or 2 days respectively (p>0.001) (Table 4). A low platelet count was also associated with higher risk, with 81% of the patients with counts under 100,000/µl being admitted compared to 13.6% of those having counts over 300,000 (p<0.0001). Lymphopenia

increased the risk; 14.7% (9/61) of the patients without versus 51.3% (58/113) of those with lymphopenia were admitted to PICU (p<0.0001). The model based on these variables correctly classified 81.5% of the PICU admitted patients and 80.5% of the non-admitted patients, and a ROC curve also showed a good discrimination power (AUC: 0.85; CI: 0.79-0.92, p<0.0001; Figure 2B).

The patients received a variety of treatment regimens and there were changes in the therapeutic approach along the study as knowledge about PIMS-TS increased. Intravenous immunoglobulin was used in 157 patients, aspirin in 126, steroids in 108, and tocilizumab in six. In addition, patients received antibiotics (120), anticoagulants (39), and inotropes (45). They remained in the hospital for a median of 8 days (IQR: 6-12), and those admitted to PICU or having acute cardiac alterations remained for longer (12 and 9.5 days respectively versus 7 days, p<0.0001 in each case).

Patients were re-examined immediately before or after hospital discharge (13 to 60 days after disease onset). The platelet count increased significantly both in PICU admitted (from 162,367 ± 15,261 to 496,876 ± 28,649 platelets/µl, n=63, p<0.0001, paired t test) and non-admitted patients (from 275,925 ± 16,986 to 520,134 ± 18,705 platelets/µl, n=97, p<0.0001). Fifty eight percent of the patients (93/160) had more than 450,000 platelets/µl at this examination. Also, an improvement was observed in most echocardiogram parameters (Table 5), including the shortening fraction, which showed a mean of 31.6 ± 0.90 % during PICU admission and 39.1 ± 0.87 % (n=44 patients, p<0.0001, paired t test) in the follow-up study.

Discussion

As reported by others (3–5,7–9), we have seen a rise in hospital admissions of children with KD clinical manifestations during the SARS-CoV-2 pandemic. Although epidemiological data on the prevalence of KD in Argentina are lacking, the two centers of reference for KD that have organized the present study contributed 63 cases between March 2020 and May 2021,while they received 7 to 9 KD cases each per year between 1976 to 2019 (unpublished data).

Our study shows a large overlap between the clinical signs and laboratory data of PIMS-TS, KD, and KSS. The clinical similarities between PIMS-TS, KD, and KSS, their similar response to immunomodulatory treatment, and previous hypothesis about viral triggers for KD, give support to the theory that PIMS-TS is part of a spectrum of KD-related conditions or a specific form of KD triggered by SARS-CoV-2 (19,20), yet, evidence in this regard is incomplete (21–25). In typical KD, 80% of the patients have less than 5 yo, whereas our patients had a median age of six, as it has been observed in incomplete and atypical KD, and in KSS (13,14,19). This is consistent with previous studies which reported an even higher median age than ours -between 8 and 10 years old- for PIMS-TS patients (6,9). KSS is a severe form of presentation of KD and was observed in 14% of our cases, which contrast with 2-7% of KD cases showing KSS in prepandemic studies (14). Our data are in agreement with previous works showing that PIMS-TS resembles incomplete forms of KD and leads to severe outcomes more frequently than KD (19,20).

Our data also agree with previous studies showing myocardial dysfunction, coronary artery alterations, and shock/severe hypotension in an elevated proportion of patients (26,27). Patients with myocardial dysfunction, expressed as left ventricle motility alterations, reduction of the

shortening fraction, and elevation of plasmatic cardiac markers, required PICU admission, inotropes, and mechanical ventilation more commonly than patients without myocardial dysfunction, in concordance with data from a recent multicenter regional study performed on 98 patients (27). A meta-analysis based on 196 publications found ECG alterations in 27%, myocardial dysfunction in 52%, coronary artery alterations in 15%, shock in 53%, and PICU admission in 75% of patients (26). These figures are in general agreement with our data, however, we observed a lower proportion of severe outcomes like myocardial dysfunction (48%), shock/severe hypotension (29%), and requirement of PICU admission (38%), although 75% of our patients admitted to PICU showed echocardiogram alterations including mitral valve insufficiency, pericardial effusion and left ventricular dysfunction as shown by a reduced shortening fraction. Moreover, we had only one death (<1% of cases), which is within the mortality rate reported in studies from high income countries (4,7–9), and contrast with the mortality rates above 4% observed in other studies from Latin America and the Caribbean (28,29). Why mortality and severe outcomes were relatively low in the present study is unclear. However, the delayed initiation of the first wave relative to European countries, previous experience from the organizing centers in the management of KD, and early dissemination of treatment directives to associated centers, may have helped.

Our data agree with those of other series suggesting that lymphopenia, thrombocytopenia, anemia, hypoalbuminemia, and increases in proBNP, troponin, C reactive protein, procalcitonin, ferritin and D-dimer, relate to more severe outcomes (3,4,7). We have been able to study the independent effect of some variables on the risk of developing severe illness as reflected in the need for admission to PICU. Lymphopenia and thrombocytopenia, which are very common in PIMS-TS (4,7,8,30,31) were associated with a higher risk of PICU admission. Also, an early diagnosis or introduction of treatment, likely related to rapid disease progression, are associated with higher risk of PICU admission. Additional variables may also have predictive value. We have seen a 10-fold increase of plasmatic proBNP in patients that required PICU admission. Previous studies showed that proBNP increases markedly in incomplete KD and is useful to evaluate the progression of KSS (32). Since proBNP determination wasn´t available in all the participating centers, we could not directly address its predictive value for PICU admission. However, the data suggest that, together with variables that assess myocardial function, it could alert about the need for IVIG/steroids treatment and admission in PICU.

The patients were managed differently along the study as publications about PIMS-TS management emerged. Although there is consensus about the need of immunomodulatory treatment (33), whether there is a better treatment is still debated (6,34,35). Patients with myocardial dysfunction, shock and/or coronary artery alterations received IVIG and methylprednisolone pulses, anticoagulants, and hemodynamic support as needed following published guidelines (36). We did follow-up studies for up to two months from hospital discharge in most of the enrolled patients. As observed in KD, we observed thromobocytosis (platelet count over 450000 per µl) in 58% of the cases. Moreover, only 11% of the patients showed cardiac and/or coronary alterations by two months after discharge, which agrees with previous studies reporting a normalization of cardiovascular function by 3 to 6 months (37,38).

The present study has several limitations, including the uneven availability of laboratory determinations in the participating centers, echocardiographic examinations were performed with different equipment and by different operators, admission policies may have differed

between participating centers, and management guidelines were modified during the study as data were gathered and publications about PIMS-TS emerged. In addition, because laboratory data were recorded at different times after admission and progression to severe outcomes was commonly very fast, the predictive value of the logistic regression model needs to be validated in an independent sample.

In conclusion, in our country, PIMS-TS cases showed clinical manifestations that overlap incomplete and typical forms of KD, and were often associated with severe outcomes including multisystem inflammation, myocardial dysfunction, shock, and PICU admission, but with a very low death rate. The rate of severe outcomes was comparable with that of high-income countries, likely because the first cases were detected early during the pandemic by personnel trained in the diagnosis and management of KD, allowing the rapid dissemination of guidelines for diagnosis and management among the participating centers. Together with other published studies, this work helps to better understand this novel clinical entity.

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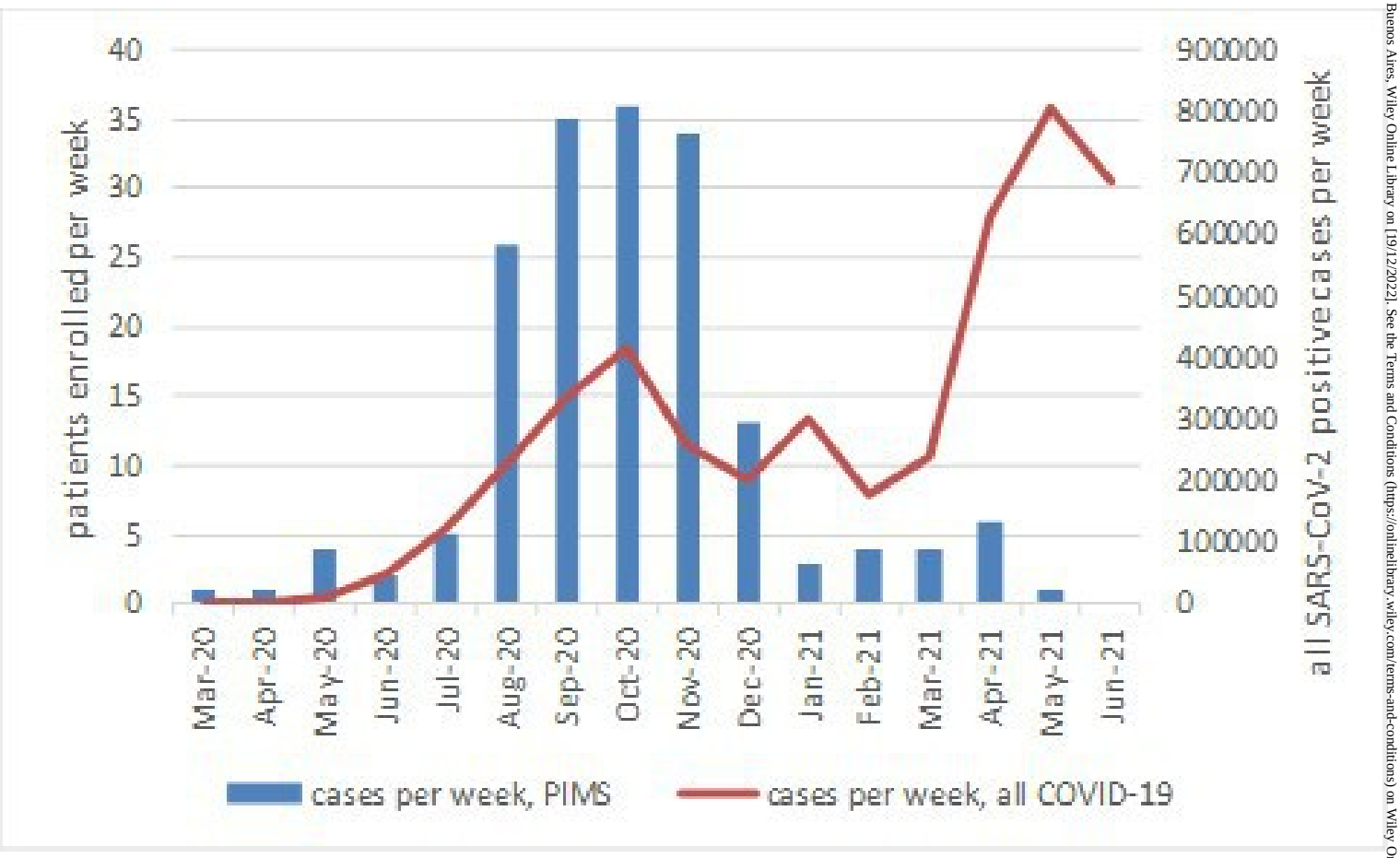
Figure 1. Time course of hospital admissions of PIMS-TS cases in all participating centers compared with total COVID-19 cases reported in Argentina per week. Data on total COVID-19 cases were taken from: Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian and Max Roser (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' [Online Resource]

Figure 2. Model parameters and ROC curve. A. Beta coefficients and formula of the model obtained by logistic multiple regression on the data. B. ROC curve showing the trade off between sensitivity and specificity of the model.

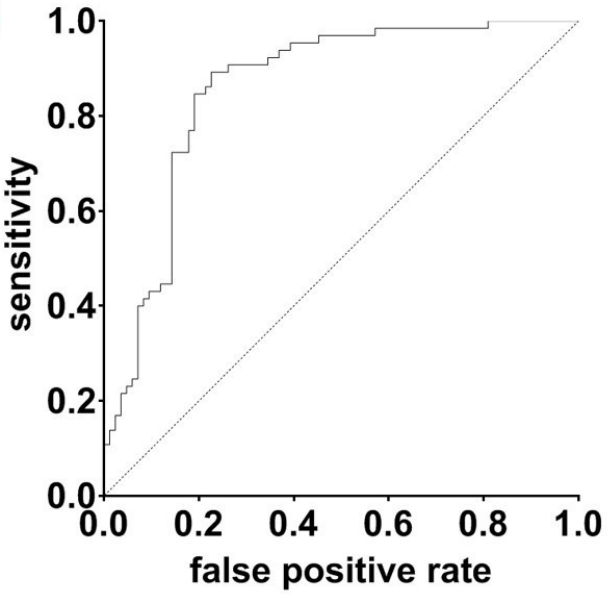


PED_15431_Figure_1_cases_per_week.jpg

A

	beta coefficient
intercept *(i)*	2.102371 *(i')*
days from first symptoms to treatment *(a)*	-0.684299 *(a')*
platelet count (data/10000) *(b)*	-0.068301 *(b')*
lymphopenia *(c)*	1.876375 *(c')*
rash *(d)*	-1.333613 *(d')*
days with fever before diagnosis *(e)*	0.449737 *(e')*
SARS-CoV-2 association *(f)*	0.747519 *(f')*
age *(g)*	-0.006403 *(g')*
logit(p) = *i'*+(*a'*a*)+(*b'***b*)+(*c'***c*)+(*d'***d*)+(*e'***e*)+(*f'***f*)+(*g'***g*)**	

B



PED_15431_Figure 2 high resolution.jpg

Table 1. Demographic, clinical, laboratory and echocardiogram data for PICU admitted and non-admitted patients.

	All patients	Stratification by PICU admission		
		PICU absent	PICU present	*p*
n	176	109	67	
Age at presentation (mo)	72 (37-117)	70 (29-114)	84 (51-118)	NS
Male/Female (ratio)	104/72 (1.44)	66/43 (1.53)	38/29 (1.31)	NS
Weight (kg)	22.3 (16-36)	22.6 (14-35)	22 (18-40)	NS
Comorbidities	28/176 (15.9%)	14/109 (12.8%)	14/67 (20.9%)	NS
Virology				
SARS-CoV-2 PCR positive before admission	37/174 (21%)	19/107 (18%)	18/67 (27%)	NS
SARS-CoV-2 IgM positive at admission	47/167 (28%)	21/102 (21%)	26/65 (40%)	**0.0082**
SARS-CoV-2 IgG positive at admission	124/170 (73%)	69/103 (67%)	55/67 (82%)	**0.0347**
SARS-CoV-2 temporally associated	149/176 (85%)	88/109 (81%)	61/67 (91%)	0.0847
Clinical presentation				
PIMS-TS	143/176 (81.2%)	79/109 (72%)	64/67 (95%)	**<0.0001**
Kawasaki disease	144/176 (81.8%)	96/109 (88.1%)	48/67 (71.6%)	NS
incomplete	86/144 (60%)	61/96 (63%)	25/48 (52%)	NS
typical	51/144 (35%)	33/96 (34%)	18/48 (37%)	NS
atypical	7/144 (5%)	2/96 (2%)	5/48 (10%)	**0.0412**
Kawasaki shock syndrome	25/176 (14%)	1/109 (0.9%)	24/67 (36%)	**<0.0001**
macrophage activation syndrome	2/176 (1.1%)	1/109 (0.9%)	1/67 (1.5%)	NS
Clinical outcomes				
days to initiation of treatment	5 (4-7) *[156]*	6 (5-7) *[90]*	4 (3-5.25) *[66]*	**<0.0001**
total duration of admission (days)	8 (6-12) *[176]*	7 (5-9) *[109]*	12 (8-19) *[67]*	**<0.0001**
shock / hypotension	51/176 (29%)	6/109 (5.5%)	45/67 (67%)	**<0.0001**
inotropes	45/176 (26%)	2/109 (1.8%)	43/67 (64%)	**<0.0001**
mechanical ventilation	29/176 (16.5%)	--	29/67 (43%)	**<0.0001**
PICU admission	67/176 (38%)	--	--	
Main clinical manifestations				
fever	176/176 (100%)			
fever days to diagnosis	4 (3-6) *[172]*	5 (3-6) *[106]*	4 (2-5) *[66]*	**0.0165**
abdominal pain / diarrhea	139/176 (79%)	79/109 (72.5%)	60/67 (90%)	**0.0075**
rash	124/176 (70.5%)	85/109 (78%)	39/67 (58%)	**0.0066**
conjunctival injection	109/176 (62%)	68/109 (62%)	41/67 (61%)	NS
oral mucuous membrane changes	91/176 (52%)	59/109 (54%)	32/67 (48%)	NS
swollen hands and feet	63/176 (36%)	44/109 (40%)	19/67 (18%)	NS
periungual desquamation	46/173 (26.6%)	30/108 (28%)	16/65 (25%)	NS
lymphadenopathy	50/176 (28%)	33/109 (30%)	17/67 (25%)	NS
pneumonitis or pneumonia	16/176 (9%)	5/109 (4.6%)	11/67 (16%)	**0.0131**
fever and coronary artery alterations	6/176 (3.4%)	1/109 (0.9%)	5/67 (7.5%)	**0.0304**
keratitis	4/176 (2.3%)	0/109 (0%)	4/67 (6%)	**0.023**
Main laboratory findings				
lymphocyte count / µl	1546 (854-2599) *[172]*	1958 (1198-3455) *[106]*	903 (579-1692) *[66]*	**<0.0001**
lymphopenia	113/174 (65%)	55/107 (51%)	58/67 (87%)	**<0.0001**
platelet count *10^3 / ul	183 (122-308) *[175]*	231 (142-371) *[108]*	140 (83-197) *[67]*	**<0.0001**
hemoglobin (g/dl)	10.6 (9.7-11.7) *[172]*	10.9 (10-11.75) *[105]*	10.3 (9.1-11.3) *[67]*	**0.0069**
hematocrit (%)	31.7 (29-34.7) *[175]*	32 (30-35) *[108]*	30 (27-33) *[67]*	**0.0012**
C-reactive protein (mg/l)	154.8 (96-254.5) *[174]*	135 (69-231) *[107]*	196 (127-270) *[67]*	**0.002**
procalcitonin (ng/ml)	1.93 (0.57-7.1) *[115]*	0.88 (0.23-2.8) *[62]*	6.7 (1.8-20) *[53]*	**<0.0001**
ferritin (ng/ml)	401 (210-785) *[155]*	290 (154-641) *[93]*	578 (359-1122) *[62]*	**<0.0001**
elevated transaminases	57/176 (32%)	31/109 (28%)	26/67 (39%)	NS
total bilirubin (mg/dl)	0.38 (0.23-0.69) *[152]*	0.33 (0.2-0.5) *[94]*	0.5 (0.3-1.1) *[58]*	**0.001**
albumin (g/dl)	3 (2.6-3.6) *[158]*	3.3 (2.8-3.7) *[91]*	2.7 (2.4-3.3) *[67]*	**<0.0001**
K+ (mEq/l)	3.8 (3.5-4.2) *[166]*	4 (3.5-4.3) *[99]*	3.7 (3.4-4) *[67]*	**0.0096**
Na+ (mEq/l)	134 (132-137) *[170]*	135 (132-138) *[103]*	133 (130-136) *[67]*	**0.0042**
pro brain natriuretic peptide (pg/ml)	2206 (447-7862) *[115]*	614 (248-1867) *[62]*	6870 (3086-20840) *[53]*	**<0.0001**
troponin (pg/ml)	24.4 (9-100) *[159]*	11.7 (6.7-52.3) *[95]*	58 (21-141) *[64]*	**<0.0001**
D-dimer (ng/ml)	2630 (1520-4115) *[145]*	1990 (1235-3503) *[86]*	3910 (2245-6210) *[59]*	**<0.0001**
Electrocardiographic findings				
sinus tachycardia	49/160 (31%)	25/100 (25%)	24/60 (40%)	0.0529
conduction block (any)	10/176 (5.7%)	2/107 (1.8%)	9/67 (13.4%)	**0.0034**
repolarization abnormalities	22/148 (15%)	6/95 (6.3%)	16/53 (30%)	**0.0002**
Echocardiogram findings				
any echocardiogram alteration	85/172 (49.4%)	35/105 (33%)	50/67 (75%)	**<0.0001**
mitral valve insufficiency	52/172 (30%)	17/105 (16%)	35/67 (52%)	**<0.0001**
tricuspid valve insufficiency	29/172 (17%)	13/105 (12%)	16/67 (24%)	0.0609
aortic valve insufficiency	3/172 (1.7%)	0/105 (0%)	3/67 (4.5%)	0.0575
MAPSE (mm)	12 (10-13.4) *[85]*	12 (10.5-14) *[45]*	11.5 (10-13) *[40]*	NS
TAPSE (mm)	19 (16-20) *[82]*	18 (15-20) *[47]*	20 (16-20.5) *[35]*	NS
ventricular dilatation	13/172 (7.6%)	1/105 (1%)	12/67 (18%)	**<0.0001**
fractional shortening (%)	36 (30.5-41) *[125]*	38 (35-42.6) *[68]*	32 (28.5-36.5) *[57]*	**<0.0001**
left ventricular wall motion alterations	23/167 (14%)	4/104 (3.8%)	19/63 (30%)	**<0.0001**
pericardial effusion	34/172 (19.8%)	12/105 (11%)	22/67 (33%)	**0.0008**
any coronary artery alteration	32/173 (18.5%)	19/106 (18%)	13/67 (19%)	NS

Data are median (IQR) *[n],* or number of cases/n (%). Statistical comparisons were performed with the Mann Whitney U test or Fisher Exact test as appropriate.

Table 2. Demographic, clinical, laboratory and echocardiogram data for patients with and without acute myocardial alterations.

	Stratification by acute myocardial involvement		
	without involvement	**with involvement**	***p***
n	**92**	**84**	
Age at presentation (mo)	71 (34.25-113)	73.5 (44.5-118)	NS
Male/Female (ratio)	56/36 (1.56)	48/36 (1.33)	NS
SARS-CoV-2 temporally associated	76/92 (83%)	73/84 (87%)	NS
Clinical presentation			
PIMS-TS	72/92 (78.3%)	71/84 (84.5%)	
Kawasaki disease	73/92 (79.3%)	71/84 (84.5%)	NS
Kawasaki shock syndrome	2/92 (2.2%)	23/84 (27.4%)	**<0.0001**
Clinical outcomes			
total duration of admission (days)	7 (5-10)	9.5 (7-14)	**<0.0001**
shock / hypotension	15/92 (16%)	36/84 (43%)	**<0.0001**
inotropes	7/92 (7.6%)	38/84 (45%)	**<0.0001**
mechanical ventilation	6/92 (6.3%)	23/84 (27.4%)	**0.0002**
PICU admission	15/92 (16.3%)	52/84 (62%)	**<0.0001**
deaths		1/84 (1.2%)	
More common clinical manifestations			
fever	92/92 (100%)	84/84 (100%)	NS
abdominal pain	69/92 (74.2%)	70/84 (83.3%)	NS
rash	62/92 (66.7%)	62/84 (73.8%)	NS
conjunctival injection	49/92 (52.7%)	60/84 (71.4%)	**0.0194**
oral mucuous membrane changes	40/92 (43%)	51/84 (60.7%)	**0.0244**
swollen hands and feet	33/92 (35.5%)	30/84 (35.7%)	NS
lymphadenopathy	22/92 (23.7%)	28/84 (33.3%)	NS
periungual desquamation	20/92 (21.5%)	26/81 (32.1%)	NS
irritability	20/92 (21.5%)	14/84 (16.7%)	NS
pneumonitis or pneumonia	3/92 (3.3%)	13/84 (15.5%)	**0.0071**
Main laboratory findings			
lymphocyte count / µl	1683 (1019-3062) *[90]*	1125 (686-2246) *[82]*	**0.0029**
lymphopenia	54/92 (58.7%)	59/82 (72%)	NS
platelet count *10^3/ µl	213 (124-334) *[91]*	156 (114.25-226) *[84]*	**0.0127**
hemoglobin (g/dl)	10.8 (10-11.8) *[88]*	10.25 (9.4-11.4) *[84]*	**0.0131**
hematocrit (%)	32.2 (30-35) *[91]*	30.2 (28-33.5) *[84]*	**0.0027**
C-reactive protein (mg/l)	135.4 (64.9-240.2) *[92]*	182 (115.6-271.3) *[82]*	**0.0088**
procalcitonin (ng/ml)	0.88 (0.24-3.2) *[54]*	3.2 (1.55-7.43) *[65]*	**0.001**
ferritin (ng/ml)	330 (145.5-701.5) *[81]*	491.5 (276-839.5) *[74]*	**0.019**
elevated transaminases	29/92 (31.2%)	28/84 (33.3%)	NS
total bilirubin (mg/dl)	0.35 (0.2-0.63) *[79]*	0.47 (0.28-0.78) *[73]*	**0.0231**
albumin (g/dl)	2.9 (2.5-3.5) *[81]*	3.2 (2.7-3.6) *[77]*	0.0771
K+ (mEq/l)	3.99 (3.5-4.2) *[84]*	3.75 (3.4-4) *[82]*	NS
Na+ (mEq/l)	135.5 (132.3-138.8) *[88]*	133 (130-136.3) *[82]*	**0.001**
pro brain natriuretic peptide (pg/ml)	538 (234.6-2539) *[49]*	4341 (1115-9000) *[66]*	**<0.0001**
troponin (pg/ml)	13 (6.9-79.5) *[81]*	38.9 (10.7-148.5) *[78]*	**0.0025**
D-dimer (ng/ml)	2199 (1344-3780) *[70]*	3032 (1966-4588) *[75]*	**0.0185**
Electrocardiogram findings			
sinus tachycardia	7/81 (8.6%)	42/79 (53.2%)	**<0.0001**
conduction block (any)	1/92 (1.1%)	10/82 (12.2%)	**0.0033**
repolarization abnormalities	2/76 (2.6%)	20/72 (27.8%)	**<0.0001**
Echocardiogram findings			
mitral valve insufficiency	7/91 (7.7%)	45/81 (55.5%)	**<0.0001**
tricuspid valve insufficiency	5/91 (5.5%)	24/81 (29.6%)	**<0.0001**
aortic valve insufficiency	0/91 (0%)	3/81 (3.7%)	NS
MAPSE (mm)	13 (11-14.75) *[36]*	11 (9.5-13) *[49]*	**0.0041**
TAPSE (mm)	19 (16-20) *[38]*	18 (15.5-20.5) *[44]*	NS
ventricular dilatation	0/91 (0%)	13/81 (16%)	**<0.0001**
fractional shortening (%)	38 (35-42) *[63]*	32.5 (28-38) *[66]*	**<0.0001**
left ventricular wall motion alterations	0/90 (0%)	23/77 (29.9%)	**<0.0001**
pericardial effusion	1/91 (1.1%)	33/81 (40.7%)	**<0.0001**
any coronary artery alteration	14/92 (15.2%)	18/81 (22.2%)	NS

Data are median (IQR) [n], or number of cases/n (%). Statistical comparisons were performed with the Mann Whitney U test or Fisher Exact test as appropriate.

Table 3. Multiple regression analysis

Variable	OR [95% CI]	p
days from first symptoms to treatment	0.49 [0.32-0.70]	0.0004
platelet count (data/10000)	0.93 [0.89-0.96]	0.0002
lymphopenia	6.27 [2.21-20.95]	0.0015
rash	0.24 [0.09-0.62]	0.0042
days with fever before diagnosis	1.57 [1.11-2.32]	0.0154
SARS-CoV-2 association	2.18 [0.58-8.76]	0.25
age	0.99 [0.98-1.01]	0.33

Odds ratios and 95% confidence intervals, for all the variables included in the logistic model, and statistical significance of their contribution to the model.

Table 4. Relationship between changes in individual variables with predictive value according to the logistic model and probability of PICU admission.

	variable	patients admitted to PICU/n patients	% admitted	
	platelet count (platelets/ul)			
a	>300000	6/45	13.33%	
b	<300000	61/130	46.90%	**p<0.0001 (a vs b)**
c	<200000	54/98	55.10%	
d	<100000	22/27	81.50%	**p<0.0145 (c vs d)**
	days from first symtoms to treatment			
a	7 or more	11/42	26.20%	
b	four or less	37/58	63.80%	**p=0.0003 (a vs b)**
c	three or less	19/30	63.30%	
d	two or less	11/12	91.70%	
	lymphopenia			
	without	9/61	14.75%	
	with	58/113	51.30%	**p<0.0001**
	rash			
	without	28/52	53.80%	
	with	39/124	31.45%	**p=0.0066**
	days with fever before diagnosis			
a	7 or more	6/24	25.00%	
b	four or less	41/92	44.56%	
c	three or less	32/65	49.23%	
d	two or less	18/33	54.54%	**p=0.0324 (a vs d)**
	association with SARS-CoV-2			
	without	6/27	22.22%	
	with	61/149	40.94%	**p=0.0847**
	age (mo)			
a	>144	6/20	30.00%	

b	96-143	23/44	52.27%	
c	48-95	23/58	39.65%	
d	0-47	15/54	27.78%	**p=0.0213 (b vs d)**

Effects of different levels of the assessed variables on risk of PICU admission. Statistical comparisons were performed with the Fisher exact test.

Table 5. Echocardiogram data for PICU admitted and non-admitted patients during a subacute follow up.

	All patients	Stratification by PICU admission		
		PICU absent	PICU present	*p*
Electrocardiogram findings at subacute follow up				
sinus tachycardia	6/146 (4.1%)	3/89 (3%)	3/57 (5%)	NS
conduction block (any)	2/172 (1.2%)	1/106 (0.9%)	1/66 (1.5%)	NS
Echocardiogram findings at subacute follow up				
any echocardiogram alteration	18/159 (11.3%)	5/96 (5.2%)	13/63 (21%)	**0.0041**
mitral valve insufficiency	7/159 (4.4%)	3/96 (3.1%)	4/63 (6%)	NS
tricuspid valve insufficiency	5/159 (3.1%)	4/96 (4.2%)	1/63 (1.6%)	NS
aortic valve insufficiency	0/159 (0%)	0/96 (0%)	0/63 (0%)	NS
MAPSE (mm)	14 (12-15) *[79]*	14 (11-15) *[39]*	14 (12-16) *[40]*	NS
TAPSE (mm)	19 (16-22) *[83]*	19 (16-22) *[43]*	19.4 (17-22) *[40]*	NS
ventricular dilatation	1/159 (0.6%)	0/96 (0%)	1/63 (1.6%)	NS
fractional shortening (%)	39 (36-44) *[107]*	41 (37-45) *[57]*	38 (35-42) *[50]*	0.0592
left ventricular wall motion changes	2/158 (1.3%)	0/95 (0%)	2/63 (3.2%)	NS
pericardial effusion	8/158 (5.1%)	3/96 (3%)	5/62 (8%)	NS
any coronary artery alteration	4/159 (2.5%)	2/96 (2.1%)	2/63 (3.2%)	NS

Data are median (IQR) *[n],* or number of cases/n (%). Statistical comparisons were performed with the Mann Whitney U test or Fisher Exact test as appropriate.