COVID-19 Associated Hepatitis in Children (CAH-C) during the second wave of SARS-CoV-2 infections in Central India: Is it a complication or transient phenomenon.

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Abstract

Objectives: While pediatric population has largely remained free of severe COVID-19, in some cases SARS-CoV-2 infection has been associated with complications like Multiple Inflammatory Syndrome in children (MIS-C). We mention another unique presentation subsequent to asymptomatic infection of SARS-CoV-2, a transient form of hepatitis designated as COVID-19 Associated Hepatitis in Children (CAH-C). The clinical presentations, temporal association and viral parameters of the cases of CAH-C contrasting to MIS-C hepatitis are presented here.

Design: As a retrospective and follow-up observational study we reviewed all pediatric patients presenting to our hospital with acute hepatitis. Increased number of such cases of hepatitis during the second wave of SARS CoV-2 infections, where children or adolescents developing sudden onset acute hepatitis with temporal relation to SARS-CoV-2 infection and without prior liver disease or familiar etiology of acute hepatitis are described.

Results: Among 47 pediatric patients presented with hepatitis, 37 patients had features of CAH-C, they had symptoms of hepatitis only, with majority having unelevated inflammatory markers and uneventful recovery following supportive treatment. Whereas

remaining 10 MIS-C hepatitis had protracted illness, multiple system involvement, required admission to critical care, and had mortality of 30% (3/10).

Conclusion: With the emergence of newer variants of concern (VOC) including the Delta variant which has now spread to more than 60 countries and was responsible for the massive wave of COVID-19 across India, with changing presentations, CAH-C might be one of them. Such new entities need to be identified and differentiated from other emerging syndromes in children for a timely and appropriate intervention.

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the begetter of novel COVID 19 pandemic, was first identified in the Wuhan city of the Hubei province of China in December 2019, with its subsequent epicenter being recognized in Western countries, thereafter reached India during the first wave(1). Interestingly during the Initial part of the COVID 19 pandemic young children were disproportionately spared from severe illness, with predominance of asymptomatic or mild cases without a need for hospitalization(2). Later the "multisystem inflammatory syndrome in children" (MIS-C) could be linked to SARS-CoV-2 infection(3).

The first wave of the SARS-CoV-2 pandemic persisted till November 2020 accounting for large number of infections across India where children were spared of serious disease, similar to the observation from the west(4). However during the massive second wave of COVID-19 by April 2021 the cases began to rise in India, involving children with severe illnesses(5). Newer variants of concern (VOC) including the delta (B.1.617.2) variant which spread to more than 60 countries, was largely responsible for the massive upsurge in COVID-19 cases in India(6). Because of the newer variants, disease presentations varied from respiratory system to entities like MIS-C, encephalitis(7), and hepatitis in children(8).

First reports of MIS-C were observed in children and adolescents in UK in April 2020(9), which was soon followed by the detailed reports describing the features of the new entity(10). Although initial reports did not mention much about hepatitis as a one of the features of MIS-C, it was recognized in the later part of the year 2020. It has been

observed in a subset of obese children with MIS-C, that severe disease and adverse outcomes were associated with co-existing hepatitis, similar to the findings observed among adults with COVID-19(11). However, about 60% of children with MIS-C presented with hepatitis in contrast to only 20-30% adult cases following COVID 19(12). Altered Liver function has been linked to severe disease course among such admitted patients(13).

These findings indicate that age-related differences might exist in cases of hepatitis and their disease phenotypes associated with COVID-19. During active COVID-19 infection, milder disease phenotype was observed obviating the need of prolonged hospitalizations whereas more severe patterns were seen in cases with MIS-C often associated with shock, respiratory distress, chances of multi-organ failure and prolonged need for hospital admissions(14). In the current context, the effects of liver injury, underlying mechanisms and the respective dominant hepatic phenotype in children with COVID-19 may have a link with emerging VOCs including delta variant(15). Its interplay with host immune response might have a bearing on the management strategies, disease burden and various adverse outcomes(14).

During the ongoing second wave of SARS-CoV-2 infections apart from MIS-C there appeared a group of children presenting with hepatitis. The features of hepatitis were typically found among previously asymptomatic children 2-6 weeks post-COVID-19. Such hepatitis cases lacked the hallmarks of inflammation seen in MIS-C, they also outnumbered MIS-C cases, hence the study was planned to correctly identify the cases, find out its temporal relation with COVID-19 and differentiate it from the other entities.

So far as the knowledge goes, literature is lacking about the detailed account of such cases of post-COVID-19 hepatitis in pediatric or adolescent age group, as described in CAH-C, different from already familiar liver injury phenotypes described earlier in children.

Methods

Patients and Study Design: It was a retrospective and follow-up observational study of children presented with acute hepatitis during April 2021 to July 2021 at a tertiary care public hospital and Medical College in Sagar, a district in central India, which is a

dedicated COVID-19 (500 beds) center for the entire region as *shown in figure 1*. During the study period a total of 475 children within 14 years of age tested COVID-19 positive by Indian Council of Medical research (ICMR) recommended RT-PCR assay. As per the existing protocols, all the positive cases, their family members and contacts were monitored through central control command telemedicine center from the Sagar smart city control room(16). Children presented with serious symptoms including hepatitis, during post-COVID-19 illness were admitted to the hospital. A record review for all such patients was performed and follow-up information was collected from the control command center and from the hospital helpdesk center. The outline of the procedures is shown in *figure 2*.

Inclusion criteria: Children presented with clinical features and laboratory findings (elevated transaminases) suggestive of acute hepatitis during post-COVID-19 were enrolled in the study for further evaluation. Based on temporal association in relation to COVID-19, disease severity (admission in intensive care unit), inflammatory markers and presence or absence of multi-system involvement these hepatitis cases were categorized into two entities:

1) COVID-19 associated hepatitis in children (CAH-C): Children with a laboratory evidence of recent COVID-19 presenting with “sudden onset of hepatitis, elevated transaminases, non-obstructive jaundice, without history of (a) underlying liver disease (b) other known causes of acute hepatitis or (c) marked inflammatory responses”.
2) MIS-C associated hepatitis: Patients of MIS-C “Serious illness leading to hospitalization, fever (body temperature, >38.0°C) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, multi organ involvement (i.e., at least two systems), and laboratory-confirmed SARS-CoV-2 infection (positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR] or antibody test during hospitalization) or an epidemiologic link with a COVID-19” patient according to the Centers for Disease Control and Prevention (CDC)(17), presenting along-with acute hepatitis i.e. elevated transaminases(18).

Exclusion criteria: Those patients who had evidence of pre-existing liver disease, drug-induced liver damage or known cause of acute hepatitis were excluded from the study.

Laboratory investigations: SARS-CoV-2 RT-PCR was done at the ICMR recognized Virology Research and Diagnostic Laboratory (VRDL) of the hospital with the established protocols and results were recorded on the national portal. All patients presenting with hepatitis were thoroughly evaluated as per the standard protocols including complete blood counts, liver function tests, renal function tests, serum ferritin, CRP, D Dimer, LDH, myocardial enzymes, and procalcitonin in the Central clinical lab in the dedicated COVID-19 hospital of our institute. Those children with signs of acute hepatitis were further evaluated with additional tests including HbsAg, anti-hepatitis E virus (HEV) IgM, anti-hepatitis A virus (HAV) IgM, anti HCV, anti-Leptospira IgM, anti EBV IgM, anti VZV IgM, Widal test, malaria antigen, malaria antibody, antinuclear antibody (ANA), anti LKM antibody, total IgG, anti-SARS-CoV-2 IgG, dengue NS1 antigen, dengue IgM (Antibody tests were done in the department of Microbiology with ICMR recommended ELISA kits)(19), and a repeat RT-PCR for COVID-19.

Treatment: Children in the CAH-C cases (n=37), admitted in general wards were given supportive therapy consisting of anti-emetics, IV fluids, vitamins, Zinc without any requirement of oxygen administration or steroids. Those with MIS-C and hepatitis (n=10) were treated as per the ICMR recommended COVID-19 regimen for children and other supportive treatment inclusive of IVIG (n=1) in child with neurologic symptoms, steroids in all, and oxygen administration (n=3) in intensive care settings, without mechanical ventilation.

Outcomes: Survival at 4 weeks to discharge was taken as an endpoint for the assessment of the outcomes.

Statistical analysis: The data was extracted and entered in MS excel, proportions and percentages were calculated for categorical variables. The chi-square test was performed to find possible associations between the categorical variables like

association of male sex, clinical outcome with either of entities. After checking the normality of data, *t*-test was applied to compare the mean values of different baseline laboratory parameters such as age, days of hospital stay etc. For those variables not having normality Mann Whitney U test or Fischer's exact test was applied; A *p*-value of less than 0.05 was considered significant. The statistical analysis was performed using SPSS trial version 16 for windows.

Ethics approval: The follow-up and analysis work was performed after obtaining due approval of human ethics committee of the institution (Ref no. IEC/BMC/80/21).

Results

Patient characteristics: During the study period from April 2021 to July 2021 among the screened population of 15873, 475 (2.99%) children with a male to female ratio of 303: 172(1.76:1) were found to be COVID-19 RT-PCR positive. The age group of these children ranged from 4 months to 14 years with mean age of 9 ± 3 years as shown in *figure 3.a. A*mong the admitted patients, 47 presented with features of hepatitis *(Table 1)* could satisfy the inclusion criteria, 2 cases presenting with hepatitis were excluded from the study as one of them was suspected to have drug induced liver injury, other was positive for HAV infection (*figure 2)*. As per the above- mentioned criteria, 37 patients (Male: Female, 23:14) and 10 (Male: Female, 3:7) patients could be categorized into CAH-C and MIS-C respectively. The distribution of age groups for both entities is depicted in *figure 3.b* where majority belonged to 2-6 years' age group. All children had same racial characteristics.

The MIS-C cases started in mid-April 2021 and peaked around the end of May 2021, showing a decline thereafter limiting to 1 case in July first week and finally disappearing in July 3rd week, after a lag of 2-3 weeks following new COVID-19 cases disappeared in June end. The cases of CAH-C started appearing in April-end and peaked in may end and then showing a decline in trend with small number of cases (3-4) still presenting after 4 weeks of disappearance of new COVID-19 cases in the district. The relative incidences of hepatitis cases in temporal relation to COVID-19 cases have been shown in *figure 4*.

Clinical and laboratory findings:

CAH-C group: Children presented with typical symptoms of hepatitis including nausea, vomiting, loss of appetite, weakness and mild fever not exceeding 38 ºC. The frequency of symptoms is shown in *figure 5 a.* Icterus was present on examination in majority (25/37) of cases. All these children had history of COVID-19, however none of them experienced any serious or typical symptoms of COVID-19 or any significant finding on chest X-ray. The X-ray findings of CAH-C versus MIS-C have been shown in *figure 5 b*.

On laboratory investigation: 35/37 CAH-C cases had RTPCR test negative for SARS-CoV-2 by the time when admitted, majority cases (29/37) had significantly elevated transaminases (>10X upper limit of normal (ULN) with median 1326.2 (range 70-5685) U/L), serum bilirubin with median 4.05 (range 1.4-17.1) mg/dl, 25/37 had unelevated (remaining 12/37 had moderate elevation) C reactive protein (CRP), median 5.4 (range 0.70-7.9) mg/L, IL-6, median 9.7 (range 2.1-24.6.3) pg/ml (p=0.0001). Many (16/37) had elevated alkaline phosphatases 2X ULN (p= 0.29), slightly elevated total IgG levels median 1245.3 (range 551.4-1640) mg/dl, 35/37 had normal platelet counts, median 2.45 (range 0.69-7.7) /mm^3X10^3 and D-Dimer could be performed in 8/37 among them and 5 were within range. All 37 (100%) patients were positive for SARS-CoV-2, anti-N protein antibodies in high titers. All were ANA negative, anti- LKM antibody negative (available for 21/37), 8/37 (21.6%) had positive IgM antibodies for Dengue. In 21/37 (56.7%) a Widal titer of more than 1:160 for both O and H antibodies. Furthermore, anti-VZV IgM antibodies were found in 7/37 (19%) of these and anti EBV-IgM was found in 8/37 (21.6%) of them, respectively. The mean laboratory values of the groups have been depicted in *Table 2.*

Outcomes: All patients admitted were discharged with supportive treatment without any complications with mean hospital stay of 4 (± 1.0) days and remained uneventful at 4 weeks' follow-up. No mortality was reported in this group.

MIS-C with hepatitis: Children were presented with moderate to severe symptoms of COVID-19 and a persistent fever of >38 ºC made them to be hospitalized. Besides persistent fever, they had sub-conjunctival hemorrhages, cough, shortness of breath,

with features of hepatitis such as abdominal pain, loss of appetite and weakness. Of them, 3 (30%) developed ARDS and signs of multi-organ failure mainly hypotension, swelling and one of them developed signs of liver failure. One child presented with epidermal necrosis and toxic shock like picture, one with encephalitis and 5 (50%) children had features of pneumonia on chest X rays (*figure 5 b)*. All cases had admission in intensive care units. On laboratory investigation: MIS-C patients presented with hepatitis, majority (7/10) were RT-PCR test positive for SARS CoV-2 within 2-3 weeks, they had markedly raised CRP median 17.8 mg/L (p=0.0001), significantly elevated IL-6 median 134.4 pg/ml (p=0.0001) and reduced albumin levels with median 3.3 gm/dl (2.7-3.58) (p=0.116). D-Dimer level was elevated (>1.5) in all 7 cases in which it could be measured. They had reduced platelet counts in some cases, moderately elevated transaminases (ALT 40-200 U/L), normal or borderline raised serum bilirubin, mildly elevated alkaline phosphatases, and raised procalcitonin (available only for 4 cases). None were Widal or dengue IgM positive (5/5), positive ANA in 1/5 cases and positive SARS-CoV-2 antibody test in 3 /5cases. These 3 cases had a contact history with RT-PCR confirmed COVID-19 patients but were themselves RT-PCR negative for SARS-CoV-2. Among the MIS-C children having various multi-system involvement including lung disease, vasculitis, encephalitis, one child developed paralytic ileus which resolved on conservative treatment, however 3 (30%) out of 10 had an adverse outcome. These cases had protracted illness, the mean hospital stay in this group was 8 (± 1) days. on 4 weeks' post-discharge follow-up the remaining children had uneventful recovery.

Discussion

With the emergence of newer variants of concern (VOC) and recurring waves of the COVID-19 pandemic, varied symptoms and post COVID-19 complications have been observed. While, pediatric population remained largely unaffected by the horror of COVID-19 during the initial wave of SARS-CoV-2 infection, things changed for this age group in the subsequent waves. In our study on 475 COVID-19 pediatric patients during the second wave of the pandemic, 37 cases were identified with a unique presentation of acute hepatitis designated as CAH-C, whereas MIS-C could account for 10 cases.

It is worth mentioning that CAH-C cases were either asymptomatic or had milder disease course. None of them had any previous underlying morbidity. They presented 2-6 weeks after having mild symptoms or exposure to a lab-confirmed case of COVID-19 and surfaced during the peak of the second wave of COVID 19 pandemic in central India. This might just be the tip of the iceberg, owing to the fact that this is an initial and early report of such cases. A possibility of missing some other less prominent features of this entity might be there which only time will tell, since initially we were focused mainly on the most prominent presenting symptoms. There may be a possibility of increase in such cases with the spread of Delta or further variants of Concern and their spread to various regions across the globe in the anticipatory 3rd Phase of the pandemic.

Cases of CAH-C were monitored carefully for deterioration since they are observed for the first time and no guidelines were available for treatment of such cases, interestingly they responded well following supportive treatment and care without necessitating anti-viral treatment. None of them required antiviral drugs, oxygen therapy or mechanical ventilation, which was the recommended line of treatment for cases with deterioration in COVID-19(20). CAH-C cases reported were greater in older children (6-11 years) and with male preponderance. Higher expression of ACE2 receptors in cholangiocytes(21) and TMPRSS2 receptor in hepatocytes among males might be predisposing them for the liver damage(22). Interestingly, CAH-C cases had distinct immunological imprints having raised anti SARS-CoV-2 antibodies (titers >50 COI) in all the cases, negative ANA, negative anti-LKM, significant Widal titers (>1:160 O, H), along with positive dengue IgM, positive anti-EBV IgM was seen in 8/37 cases and anti-VZV IgM in 7/37 patients respectively. The multi-positivity for various infectious agents along with elevated total IgG levels were missing in children having MIS-C and are unusual for children of such young age. These findings point to skewed immune activation especially B cell stimulation giving rise to multiple antibody responses as a result of possible polyclonal B cell immune activation by some of the SARS-CoV-2 antigens. The role played by SARS-CoV-2 in CAH-C is in contrast to the polyclonal (Vβ 21.3+ CD4+ and CD8+) T-cell stimulation observed in cases of MIS-C(23). Thus, SARS-Cov-2 is a

potent immune-stimulator through molecular mimicry leading to polyclonal B cell activation exclusively in children with a self-limiting course in post COVID CAH-C cases.

Possibly of the complications seen following SARS-CoV-2 infections, MIS-C is at the more severe end hallmarked by polyclonal T- cell activation whereas CAH-C is on the milder spectra of disease course hallmarked by polyclonal B-cell activation. As of now, these antibodies in CAH-C seem to be more of an evil, rather than a virtue offering any protection. In contrast to adults, children exhibit narrow spectrum of reactivity against SARS-CoV-2 which may not be neutralizing in nature. Studies indicated that alterations in B cells responses persisting during convalescence affect the long-term immunity and may be responsible for the persistence of symptoms in COVID-19 recovered adults(24). At this point with limited experience and small number of cases, it would be premature to predict with certainty that CAH-C is a milder form of the disease. The other concern is the association of biological false positivity (BFP) in other infectious diseases which might pose a diagnostic dilemma in times where similar febrile illnesses including dengue, chikungunya and enteric fever remain endemic in developing countries. Prima facie, the findings of CAH-C do not resemble that of MIS-C(25). These cases lacked markedly elevated inflammatory markers or systemic derangements associated with COVID-19. Cases of CAH-C had a fair recovery without any mortality. On the contrary, much is already known about the MIS-C cases with hepatitis. Majority of these cases typically presented within 2-3 weeks of moderate to severe symptoms of COVID-19. Their numbers peaked earlier in comparison to the CAH-C cases.

Laboratory assessment of MIS-C cases showed significant association with markedly raised inflammatory markers, ferritin levels, elevated D-Dimer and decreased albumin levels in all cases. Laboratory data for antiviral or fever etiology (antibody tests) was limited for some cases in this group due to the fact that 3/10 children died before such evaluations could be performed. A long term follow-up is also desirable in these cases, currently beyond scope due to time limitations of the study.

Despite best of efforts including anti-viral drugs when needed, steroids in all cases, IVIG in 1 case, oxygen administration in 4 cases, and mechanical ventilation in 1 case, 30%

mortality was observed. MIS-C is already known to be associated with higher mortality and a poor survival rate **(10)**.

In conclusion, the timely recognition of the newly described entity of CAH-C, which by far may be a transient phenomenon, should enable the treating physician for timely administration of supportive therapy. Furthermore, it will also help in reducing burden on resource poor setups in the times of pandemic, since the MIS-C hepatitis cases are more associated with disease severity, increased mortality and need for hospitalization.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the study or its findings.

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Table 1: Patient characteristics of CAH-C Cases Vs MIS-C associated hepatitis cases.

Patient characteristics	CAH-C (n=36)	MIS-C (n=10)	P-value*$
Age, mean ± SD, years	6.75 (3.32)	6.2 (4.29)	0.3367 *
Male sex, No. (%)	23 (63.9%)	3 (30%)	0.077 $
Total days admitted, mean ± SD	4.64 (1.37)	8.4 (1.95)	0.0001 *
Day from contact history, mean ± SD	23.56 (6.63)	9.7 (93.74)	0.0001 *
Clinical outcomes:			
Recovered, n (%)	37 (100%)	7 (70%)	0.013 $
Death, n (%)	- (-)	3 (30%)	0.013 $
*Independent samples t-test, $ Fischer's exact test.			

Table 2: Laboratory findings of CAC-H Vs MIS-C associated hepatitis cases.

Lab values	CAH-C (n=37)	MIS-C (n=10)	P-value*
	Median (IQR)	Median (IQR)	
CRP, mg/L	4.10 (0.70, 7.90) (n=37)	17.85 (10.82, 28.42) (n=10)	0.0001
IL6, pg/ml	9.70 (4.27, 13.42) (n=37)	134.40 (34.00, 227.52) (n=10)	0.0001
Platelet, /mm^{3}X10^3	2.45 (2.10, 3.06) (n=37)	2.85 (1.35, 3.85) (n=10)	0.894
T Bil, mg/dl	5.4 (2.95, 7.15) (n=37)	0.90 (0.87, 1.37) (n=10)	0.0001
Albumin, gm/dl	3.60 (3.42, 3.67) (n=37)	3.45 (2.70, 3.77) (n=10)	0.394
AST, U/L	942.45 (301.67, 2002.05) (n=37)	85.50 (47.55, 127.90) (n=10)	0.0001
ALT, U/L	1326.25 (492.12, 2124.92) (n=37)	76.00 (44.42, 170.45) (n=10)	0.0001
Alkaline PO4, U/L	311.00 (187.40, 498.20) (n=27)	200.75 (131.12, 312.85) (n=10)	0.097
INR, ratio	1.30 (1.05, 1.52) (n=24)	1.00 (1.00, 1.39) (n=10)	0.174
	*Mann-Whitney U test		
CRP, C-reactive protein; SD, standard deviation; IL-6, interleukin-6: AST, aspartate transaminase; ALT, alanine aminotransferase; TBil, Total bilirubin; INR, international normalized ratio			

Figure 1: Geographic location of the study

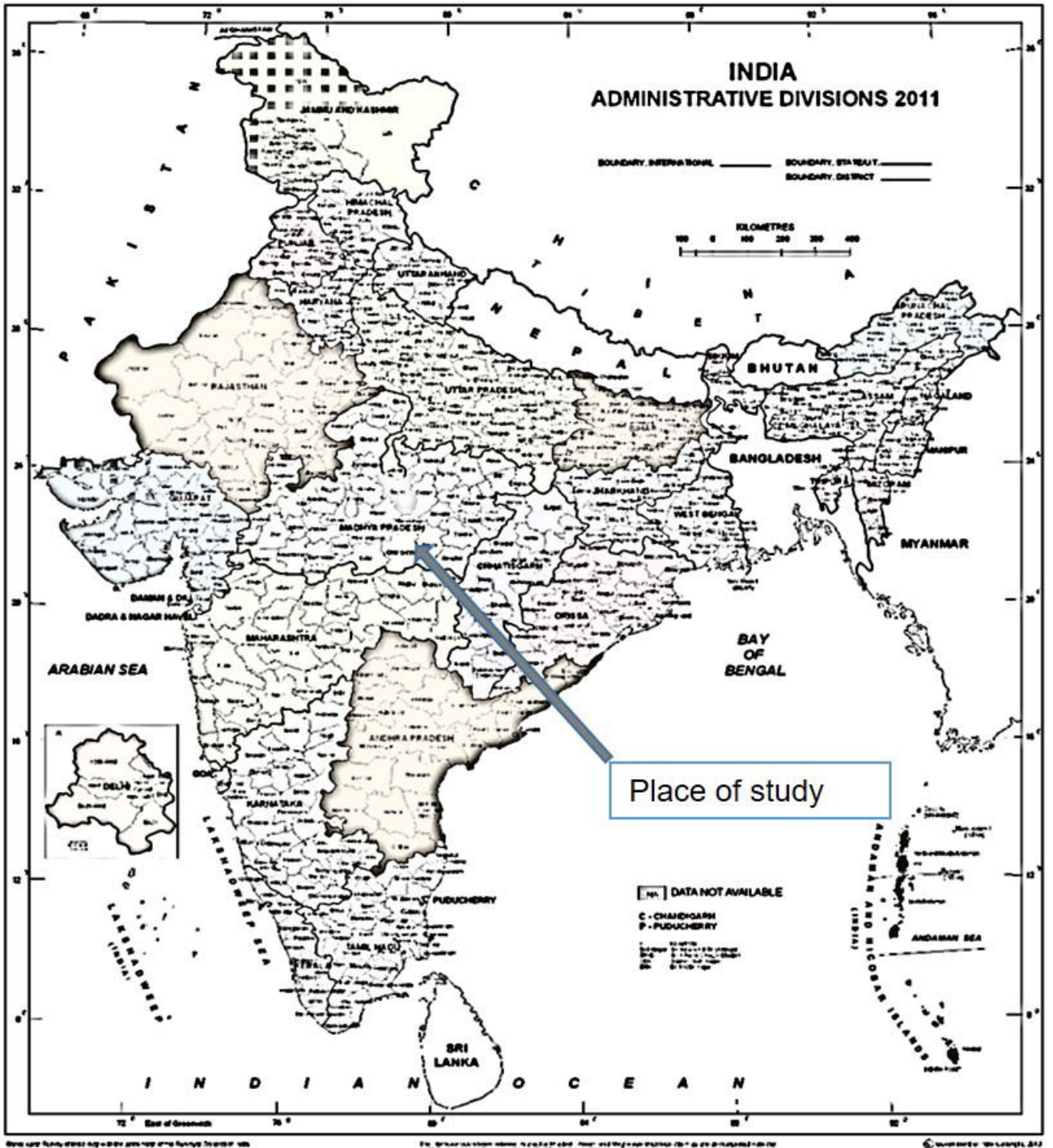


Figure 2, Study workflow and case work-up

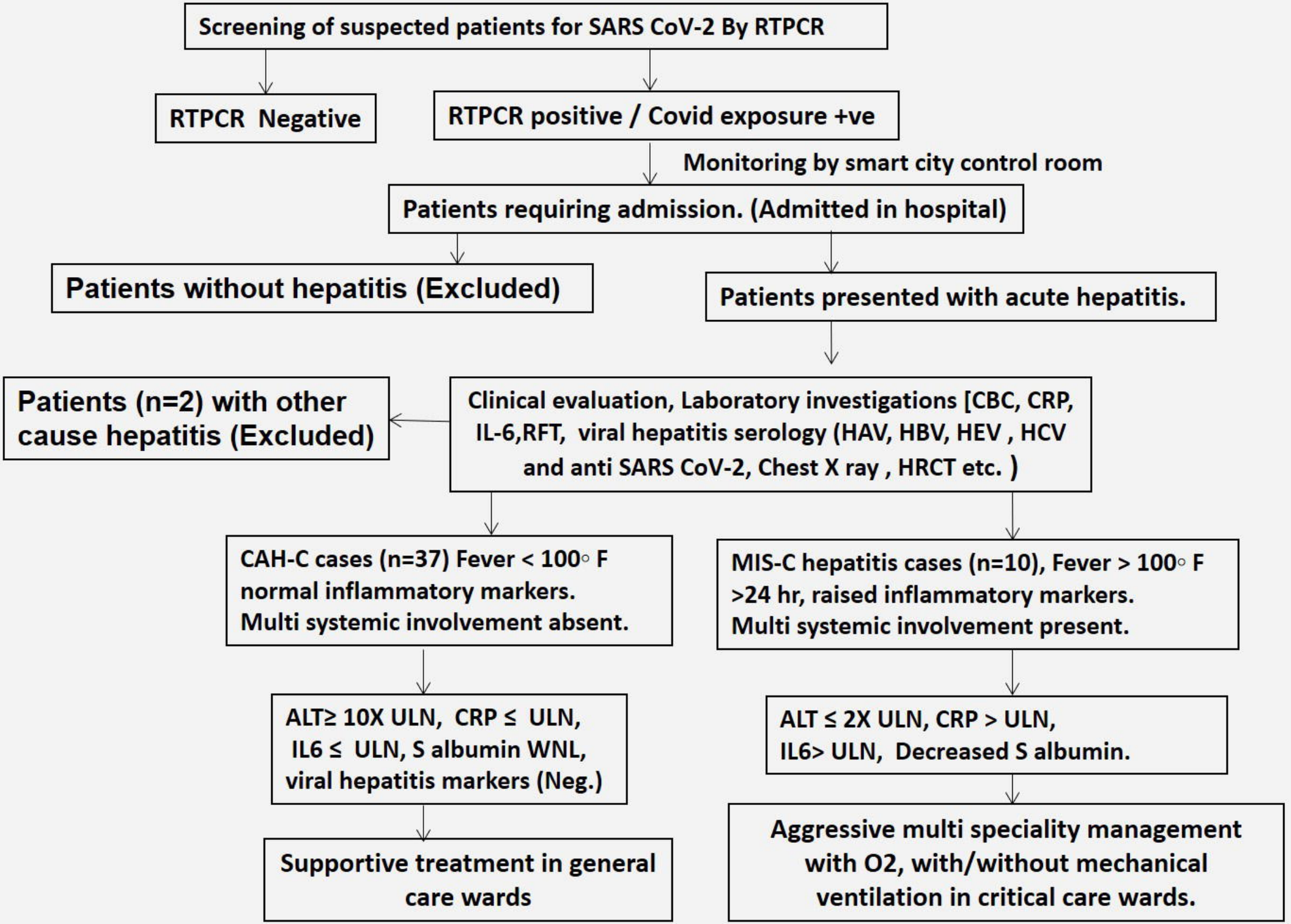


Figure 3 a : Age group distribution of total screened population vs study population

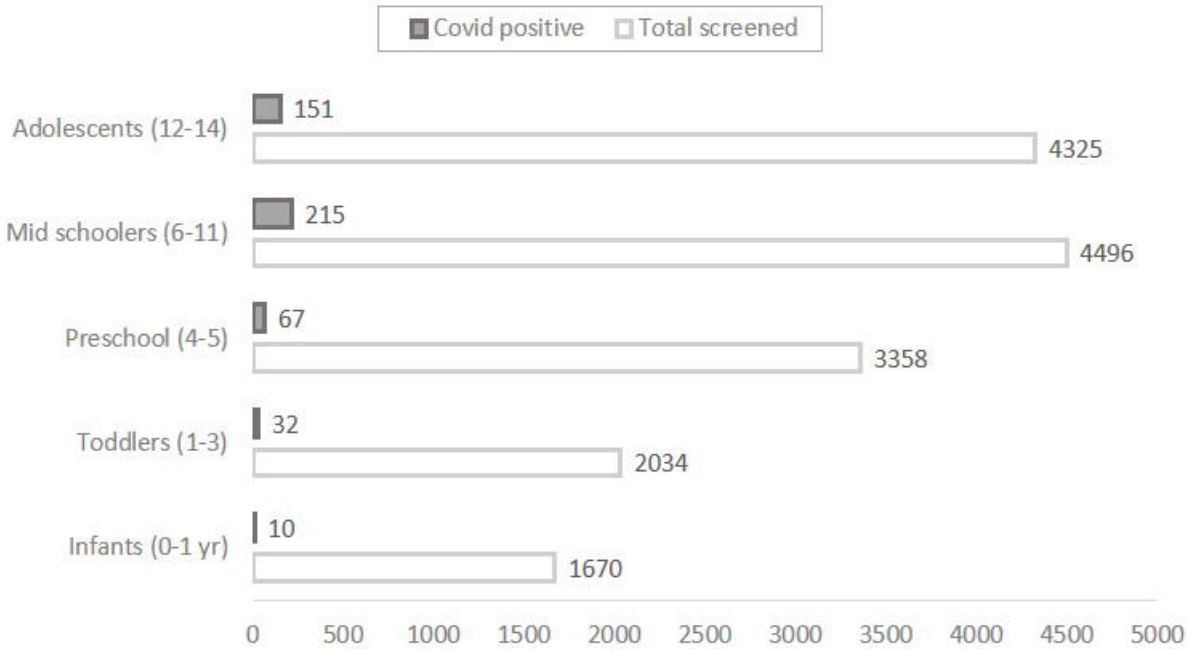


Figure 3b: Age group distribution of CAH-C Vs MIS-C cases

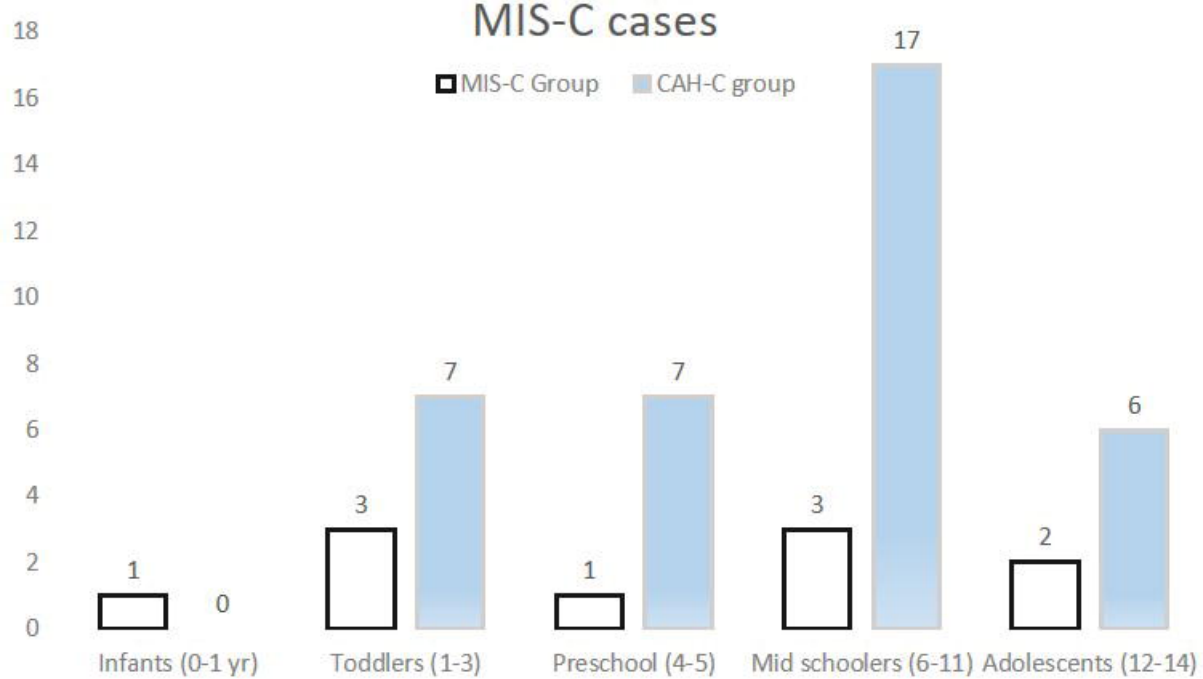
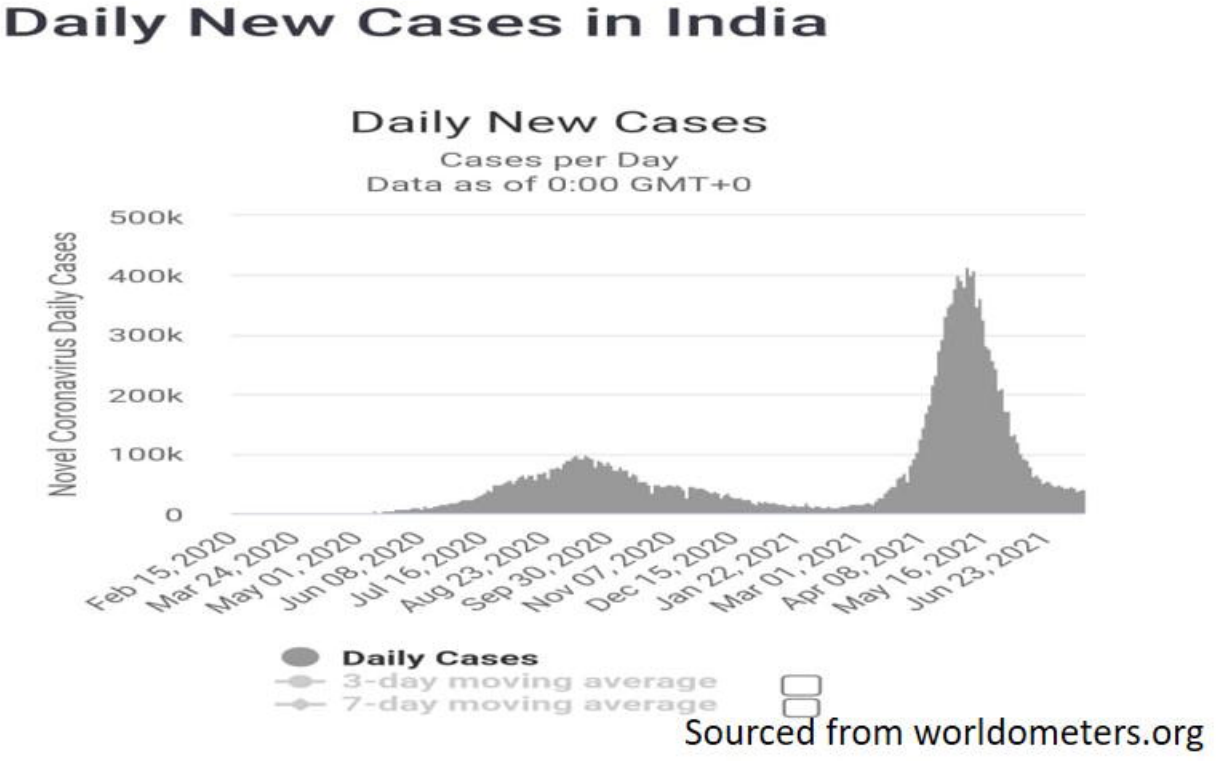


Figure 4: Relative incidences of Covid-19 new cases Vs hepatitis cases



Sourced from worldometers.org

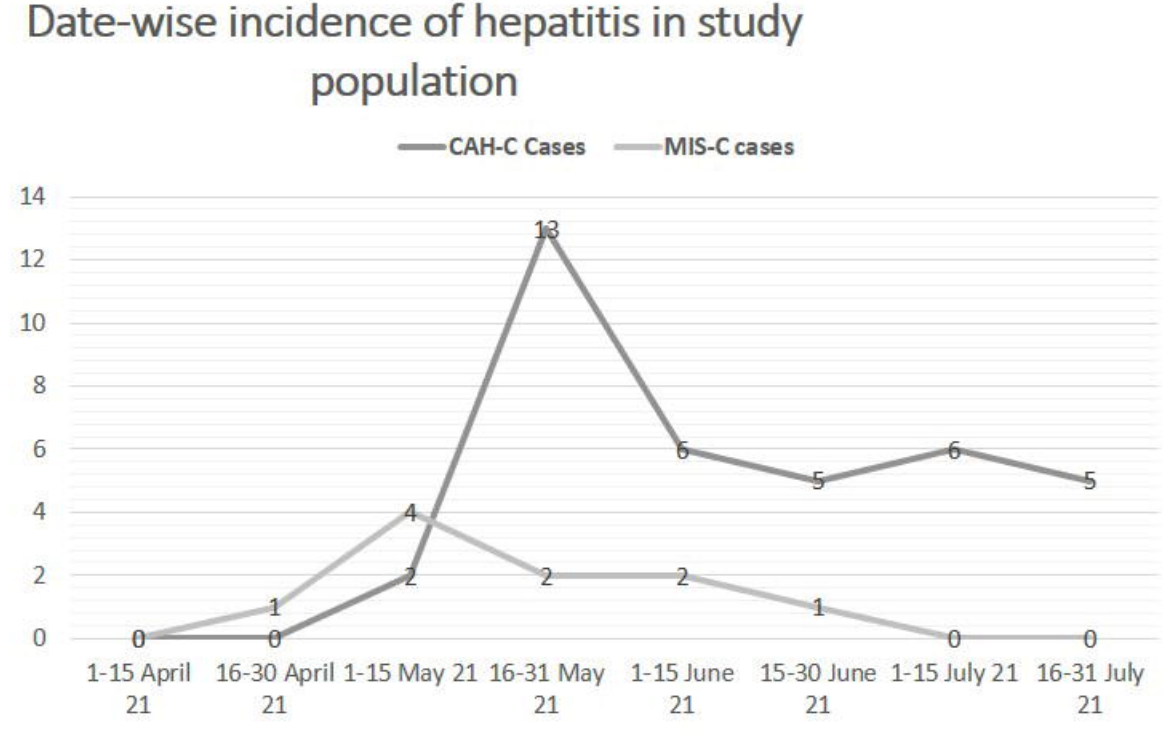


Figure 5a: Presenting signs and symptoms in CAH-C Cases

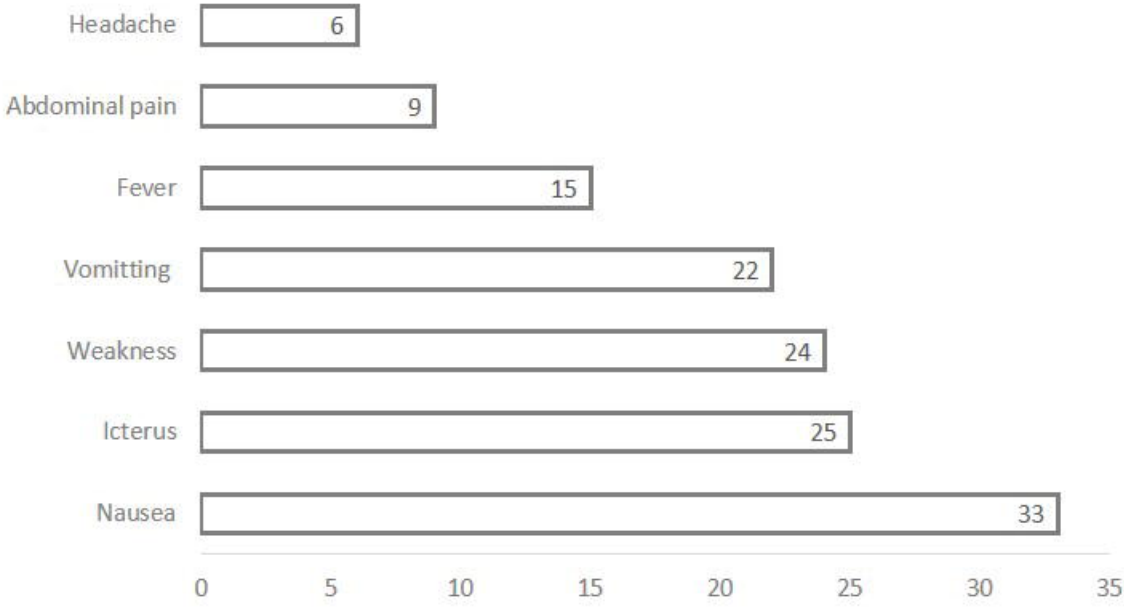


Figure 5b : X ray findings of CAH-C Vs MIS-C cases.