ARTICLE

A systematic review on the effectiveness of N-acetylcysteine in children with dengue-associated liver injury

DJ G. Leaño, & Meadina G. Cruz

OBJECTIVES: This study aimed to determine the effectiveness of N-acetylcysteine (NAC) in reversal of liver enzyme abnormalities among pediatric patients with dengue induced liver injury.

MATERIALS AND METHODS: The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) declaration was used to create this systematic review. The study population included children (<18 years old) diagnosed with dengue-associated Liver Injury and given NAC. The outcome of interest was full recovery. A search was performed in PubMed/MEDLINE, EMBASE, Google Scholar, HERDIN PLUS, WPRIM, clinicaltrials.gov, and Cochrane databases on March 2023. The New Castle-Ottawa Quality Assessment Scale was adapted for risk of bias assessment for cohort studies.

RESULTS: Three case series and one pre-post cohort study published from 2013 to 2022 were included. The studies were of acceptable quality. In two studies with overall 10 pediatric patients given NAC for dengue-related ALF, all recovered without adverse events. In one study with 4 patients given NAC, half survived with their liver function tests returning to normal values. Finally, in one comparative study, the durations of time before the liver function tests returned to normal levels, and the mortality rates between those treated with and without N-acetyl cysteine were not significantly different. All studies reported no occurrence of adverse drug reaction related to NAC.

CONCLUSION: *:* This systematic review shows limited evidence on the effectiveness of NAC in the reversal of liver enzymes among pediatric patients because of the low incidence of dengue induced liver injury seen in observational studies. Given that NAC is reported by all four studies to be accessible, effective, and with no attributable adverse events, its use can be considered. However, clinicians must still be cautioned given the limited available evidence.

KEYWORDS: *Dengue Associated Liver Injury; Dengue Hepatitis; N-acetylcysteine*

INTRODUCTION

Dengue virus is a vector borne disease transmitted by a day biting mosquito of the species Aedes aegypti and Aedes albopictus. Approximately fifty percent of the world's population is at risk of this infection, with 60-100 million symptomatic, and 20,000 deaths each year.[1-4]

In 2019, the Philippines had the highest cases ever recorded globally.[2,5] The incidence has increased dramatically, and the data has shown that dengue cases are more prevalent among children between 5-14 years old, while dengue related mortality was found among patients less than 20 years old.[1] Since then, national programs have been implemented to address the burden of disease, tailored on health promotion and advocacy, environmental control measures, and case and vector surveillance. However, the battle with dengue infection continues to challenge the public health until today.[5]

Dengue infection is a dynamic disease with levels of severity classified as: dengue with or without warning signs, and severe dengue based on clinical and laboratory parameters. The warning signs include abdominal pain or tenderness, persistent vomiting, clinical signs of fluid accumulation (ascites), mucosal bleeding, lethargy or restlessness, liver enlargement, increase in hematocrit and/or decreasing platelet count. Severe dengue is defined by at least one of the following: (a) plasma leakage that may lead to shock, (b) severe bleeding, and/or (c) severe organ impairment such as severe hepatitis (AST or ALT $\geq$ 1000); encephalitis (seizures, impaired consciousness), and myocarditis, among others.[2,6-8]

Dengue is also a multi-systemic infection, with liver involvement as the most common complication. Approximately 60-90% of patients with dengue may present with hepatitis. Elevation of liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occur in 88% and 69% of cases respectively. The mechanisms that predispose dengue infection to liver pathology include hypoxic injury, direct viral invasion, immune mediated injury, and secondary bacterial sepsis. Liver injury is defined as an elevation of at least twice the upper limit of serum ALT, whereas the clinical practice guidelines on dengue in children defined liver failure based on laboratory findings of AST elevation of more than 200 u and INR of more than 1.3..[2,6,7]

There is no specific treatment for dengue, and no effective antiviral. Even though guidelines in disease management exist, management is only supportive in nature, with emphasis on early recognition and timely intervention.[2,10] Many drugs such as chloroquine, balapiravir, celgosivir, and lovastatin have been tried in dengue-induced acute hepatic failure but were later found ineffective in treating the infection.[3]

Newer medical treatment includes N-acetyl cysteine (NAC) which was postulated to improve antioxidant defense system, its free radical scavenging activity, and its vasodilatory activity that increases oxygen delivery to the liver.[11] NAC is used as mucolytic, antidote for paracetamol overdose, and ophthalmological. It acts both as a source of reduced glutathione and directly scavenging free radicals in the body.[10] In various studies, NAC has shown promising effect among patients with dengue- induced hepatic injury.[9]

At present, there are limited data on the use of NAC in dengue-induced acute liver injury. A study conducted in Pakistan by Ishtiaq et al. highlighted the hepatic involvement in dengue infection, and stated that NAC is among the current management strategies in their locality along with intravenous hydration and symptomatic management of complications.[12] A case report in Singapore by Lim et al. showed a favorable outcome of NAC in children with dengue-associated liver failure with suggested dose of 100 mg/kg/day.[11] A case series published by Dissanayake et al. showed statistically significant reduction in liver transaminases after NAC infusion among adult patients with dengue infection.[4] Furthermore, in the study done by Tafere, et al., various case reports and series (mostly among adults) and an animal study support the role of NAC in the treatment of dengue-induced liver failure.[9] These studies highlighted the potential benefit of NAC as a definitive therapy for dengue-associated liver injury.

Despite the presence of existing studies on use of NAC in Dengue infection, the number is still limited, especially its association among children. This study may help in decreasing the disease morbidity and mortality through providing evidence-based results. This study aims to determine the effectiveness and safety of N-acetylcysteine in reversal of liver enzymes among pediatric patients with dengue induced liver injury by synthesizing available published evidence.

METHODOLOGY

The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) declaration was used to create this systematic review.

Eligibility criteria:

Types of studies. Randomized controlled trials and observational studies published until March 2023 were planned to be included. Posters, and conference abstracts were excluded. Only studies written in the English language were available.

Population. The study population included children (<18 years old) who were diagnosed with Dengue-Associated Liver Injury. Excluded are patients with other severe comorbidities.

Intervention/Exposure. N-acetyl cysteine given at any dose for the management of liver

injury.

Comparison. Standard treatment/ or no comparator group

Outcomes. In-hospital mortality, length of hospital stay, the incidence of encephalopathy post-treatment

Exclusion. Studies were excluded if outcomes were not reported clearly or cannot be computed/derived from results.

A search was performed in PubMed/ MEDLINE, EMBASE, Google Scholar, HERDIN PLUS, WPRIM, clinicaltrials.gov, and Cochrane databases on March 2023. The search terms used included: ("N-acetyl cysteine" OR NAC OR Acetylcysteine] MeSH]) AND (dengue]MeSH] OR "dengue fever" OR "dengue hemorrhagic fever") AND ("liver injury" OR hepatitis[MeSH]). Duplicate articles were removed and additional relevant articles were identified by scanning the reference lists of articles found from the original search.

Full-text articles for potential inclusion were saved in a Google drive. Extracted data were managed using Microsoft Excel and Microsoft Word. Two authors independently scanned the titles and abstracts found using the search approach described above. Papers by the same author were compared to reduce data duplication caused by duplicate reporting. The full-text articles were obtained for reports that were eligible based on the title or abstract. Full -text copies of potentially relevant papers selected by at least one author were retrieved and reviewed. Articles that met the inclusion requirements were evaluated independently by two authors, with any inconsistencies resolved through discussion. Following the PRISMA 2020 criteria, a flow diagram for the search and selection process was created.

Study name (along with first author's name and year of publication), definition of liver injury, country where the study was conducted, NAC dosage and comparison group, source from which patients or study participants were selected, study design, outcomes (mortality, length of hospital stay, rate of encephalopathy, and adverse events such as increase in prothrombin time, thrombocytopenia, and acidosis), study strengths, and limitations were extracted independently by two authors using a standardized extraction form. To ensure the correctness and consistency of the extracted data, the data extraction forms were cross-checked.

Two investigators independently assessed the studies' quality. The New Castle-Ottawa Quality Assessment Scale was adapted for risk of bias assessment for cohort studies. This scale has four dimensions: research group representativeness, suitable techniques for determining exposure, comparability of comparing analysis groups, and lower non-response bias. The quality score varied from 0 (low) to 4 (high).

The Joanna Briggs Institute quality assessment tool for case series was also used

with several indicators for inclusion criteria, definition of cases, reporting of outcomes, and follow-up of results. A score of at least 8 is considered as acceptable.

The studies were analyzed using a descriptive narrative approach wherein individual study findings were synthesized and describe the possible hypotheses on the effectiveness of NAC and its mechanism in dengue related liver injury. However, because there is heterogeneity in study design, methodology and population observed, a meta-analysis could not be performed.

RESULTS

A total of 216 articles were seen after database search and 17 duplicates were then removed. After title and abstract screening, 7 articles were determined to be for potential inclusion. After a full-text review, 3 were excluded because they were conducted on adult patients. Finally, 4 studies were included in the systematic literature review.

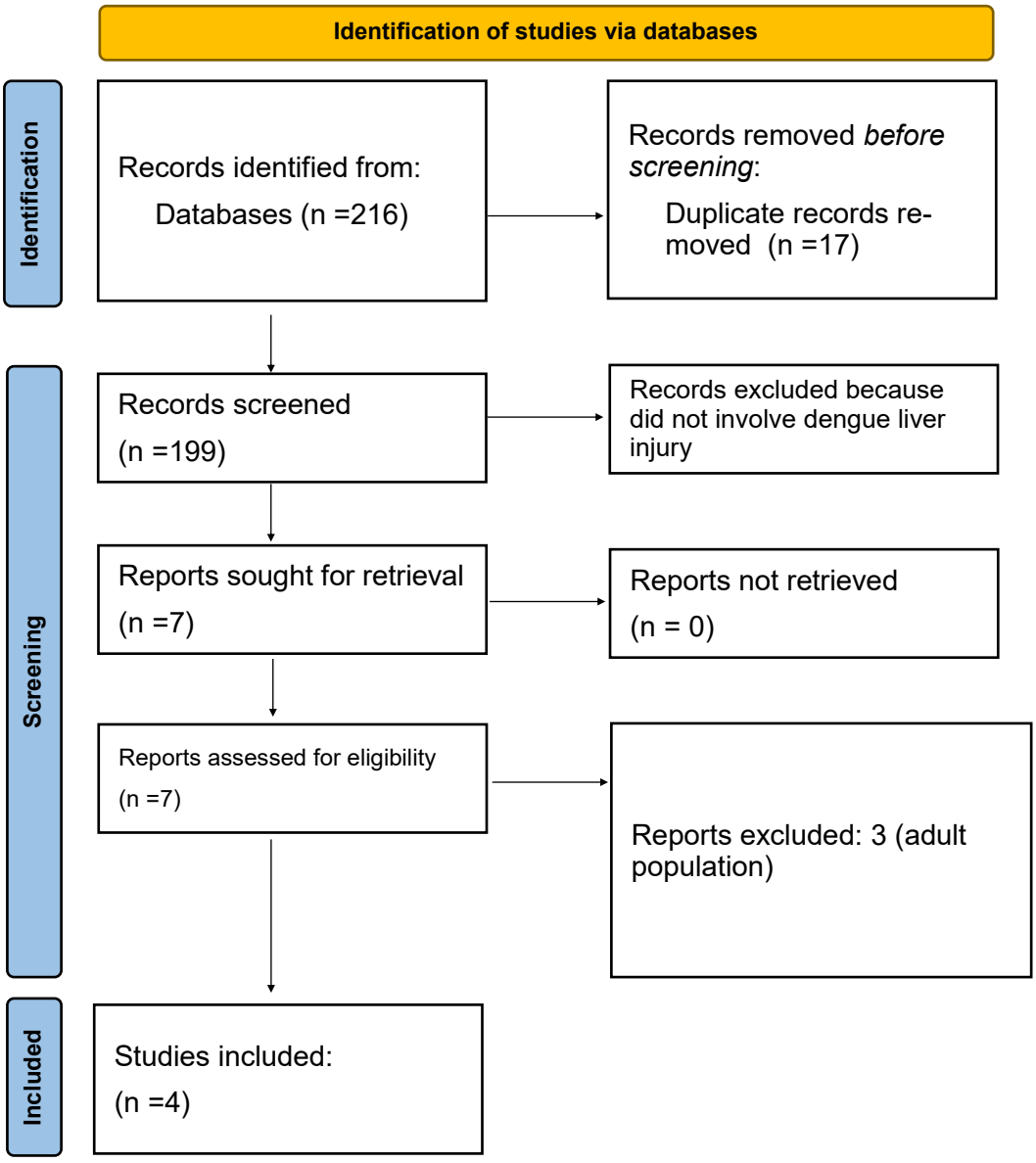

Figure 1. PRISMA Flowchart for study selection.

All four studies were conducted in Asia. Laoprasopwattana et al. (2022) was a cohort study with pre-post design while the three were case series. All studies have small sample size (3 to 23 patients given NAC). The age range in the included studies was between 6 months to 12 years. Acute liver injury was the indication for NAC use in all four studies. NAC treatment regimen was described in the study of Senanayake et al. (2013) only. Only one study was comparative in design (Laoprasopwattana et al., 2022). All studies reported on rates of complete recovery and adverse events.

Table 1. CHARACTERISTICS OF STUDIES INCLUDED IN THE STUDY

Author, year	Country	Study Design	Sample size	Sex ratio and mean age	Definition of liver injury	NAC regimen	Comparator	Outcomes
Senanayake et al. (2013)[5]	Sri Lanka	Case series	7	Not Reported, 6mo. to 12 years	Acute Liver Failure with the following signs: low GCS scores, raised transaminases and prolonged prothrombin/INR.	NAC was administered at 100 mg/kg intravenously over 24 hours.	None	Adverse events Complete recovery
Laoprasopwattana et al. (2016)[8]	Thailand	Case series	41 with 4 given NAC	1M:3F 8 years	Rapid development of severe acute liver injury with impaired synthetic function (international normalized ratio≥1.5) and encephalopathy in a patient with no history of liver disease	Details of NAC treatment not provided	None	Survival Adverse events Complete recovery
Sharma et al. (2016)[13]	India	Case series	196 with 3 given NAC	2M: 1F 5 years	Not Reported	Details of NAC treatment not provided	None	Survival Adverse events Complete recovery
Laoprasopwattana et al. (2022)[14]	Thailand	Pre-post cohort	101 with 23 given NAC	Not Reported	Not Reported	Details of NAC treatment not provided	Standard Treatment with no NAC	Adverse events Time to complete recovery

As seen in Table 2, all studies are of good quality. However, all studies have low sample size which can be attributed to low incidence of ALF in dengue fever. Nonetheless, all studies had acceptable scores.

Table 2. RISK OF BIAS ASSESSMENT OF STUDY METHODOLOGY

Joanna Briggs Institute	Clear criteria for inclusion	Standard and reliable measure-ment of condition	Valid case definition	Consecu-tive or complete inclusion of participants	Clear reporting of de-mographi cs	Clear reporting of clinical information	Clear reporting of out-comes	Conduct of statis-tical analysis	Score
Senanayake et al. (2013)[5]	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)
Laoprasop-wattana et al.	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)
Sharma et al. (2016)[13]	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)

Newcastle-Ottawa scale	Representativeness of the sample	Sample size	Comparability	Ascertainment of the exposure	Assessment of the outcome	Score
Laoprasopwattana et al. (2022)[14]	Representative of target population (1)	Small Sample size (0)	Pre-post design (1)	Record linkage (1)	Clinical diagnosis (1)	4 (Acceptable)

Four (4) studies published from 2013 to 2022 were included in this systematic review. The outcomes reported in these studies are summarized in Table 3. Senanayake et al. (2013) detailed the results of giving N-acetylcysteine (NAC) to children who had acute liver failure (ALF) complicated by dengue infection that was not caused by non-paracetamol. Retrospective analysis was done on the medical records of the patients (n=7, aged 6 months to 12 years) who had dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) exacerbated by ALF. As soon as ALF was identified based on low GCS scores, elevated transaminases, and delayed prothrombin/ INR, NAC infusion (100 mg/kg) was given. Four (4) patients showed rapid clinical improvement of their encephalopathy after receiving the first dosage of NAC (100 mg/ kg over 24 hours). After the second (n=2) and third (n=1) doses, the other 3 patients responded. In all cases, full clinical and biochemical recovery took place. NAC was found to have no adverse effects. The authors concluded that the early use of NAC to children with ALF complicating severe dengue infection resulted in a satisfactory outcome.[5]

The records of patients (n=41, aged 15 years) diagnosed with severe dengue virus infection and ALF were reviewed by Laoprasopwattana and colleagues (2016) to identify their clinical course and the outcomes of liver functions. With a death rate of 68.3%, all 41 patients with ALF experienced additional organ failure, such as acute respiratory failure (85.4%), acute kidney additional organ failure, such as acute respiratory failure (85.4%), acute kidney injury (75.6%), and active bleeding (70.7%).

On the day the patient experienced ALF, the patient's aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were at their highest. Two (2) of the 4 patients who received NAC treatment survived, and in 4 and 12 days, their liver functions returned to normal. No patient developed adverse events. It was concluded that the key contributor to ALF in patients with dengue virus infects was a deep shock that caused microcirculatory disruption in liver cells.[8]

The study of Sharma et al. (2016) described the clinical experience and results of severe hepato-neurological dengue fever sequelae. In their hospital's pediatric critical care unit (PICU), all confirmed dengue cases were examined. Of the 196 confirmed dengue cases, 4 (median age: 5.33 years, range: 0.58 to 16 years) developed ALF. Results showed that encephalopathy started 4 days (1–5) following fever in these children. Three (3) of the patients had grade IV encephalopathy, and 1 patient initially had grade III encephalopathy before advancing to degree IV. One (1) patient appeared in shock, while 2 showed symptoms of capillary leaking (ascites and bilateral pleural effusion). At presentation, enzyme levels were noticeably raised although bilirubin levels were normal in all but 1 patient. All 4 patients were mechanically ventilated. Three (3) children received supportive treatment, fluconazole, NAC, and wide spectrum antibiotics. One (1) child passed away, three children recovered and were discharged without any complications. At presentation, the deceased child experienced shock and hypoalbuminemia (2.1 g/dl). Additionally, this child had significantly more fluid retention than the responders (36.8% vs mean 2. 6%), and NAC was started 48 hours later. It was concluded that the use of NAC in ALF was advantageous. No adverse events attributable to NAC were observed. According to the author's experience, effects are beneficial, but larger studies are still required investigate more.[13]

The most recent of the 4 studies was conducted by Laoprasopwattana et al. (2022) wherein they evaluated in their pre-post cohort study the severe dengue (SD) death rates before and after the 2016 introduction of a revised SD guideline. The updated guidelines called for rigorous vital sign and intra-abdominal pressure monitoring, the release of intra-abdominal pressure in cases of abdominal compartment syndrome (ACS), and the administration of NAC in situations when the liver has failed suddenly. Review of SD patients' (age of <15 years old) medical records was done. Between 78 and 23 patients treated in the pre- and post-revised guideline periods, respectively, there were no appreciable differences in organ failure at initial admission, including severe bleeding, acute respiratory failure, acute renal injury, and acute liver failure. Following hospitalization, there was no statistically significant difference between the pre- revised guidelines (n=78) and post-revised guideline (n=23) periods in the percentage of patients

who experienced multiorgan failures (60.4% vs. 73.3%) and fatal outcomes (33.3% vs. 13.0%). The mortality rates for patients with multiorgan failure (44.1% vs. 15.8%) considerably higher in the pre-than in the post-revised guideline periods, according to subgroup analysis. In patients with acute liver failure treated with or without NAC, there were no significant differences in the lengths of time before the liver function tests returned to normal levels or the fatality rates. No NAC side effects were reported in any patient. The authors concluded that although it was determined that the updated recommendations, which call for the administration of NAC, did not prevent organ failure, doing so considerably reduced the mortality rates of patients with multiorgan failure.[14]

Table 3. OUTCOMES REPORTED IN THE INCLUDED STUDIES

Author, year	Outcomes
Senanayake et al. (2013)	No incidence of adverse events 100% of patients showed complete recovery without residual hepatic or neuro-developmental damage
Laoprasop-wattana et al. (2016)	Of the four patients treated with n-acetyl cysteine, two survived and their liver functions returned to normal levels in 4 and 12 days. No incidence of adverse events
Sharma et al. (2016)	All three recovered with no encephalopathy post-treatment and no adverse events
Laoprasop-wattana et al. (2022)	The durations of time before the liver function tests returned to normal levels, and the mortality rates in acute liver failure patients treated with and without N-acetyl cysteine were not significantly different. No incidence of adverse events

Discussion

The use of NAC as a safe and efficient treatment for dengue-induced liver impairment was endorsed by all four studies. NAC was seen to be beneficial in some pediatric patients. Specifically, in one study, NAC has been shown to be beneficial for children who have non-paracetamol-induced liver failure.[5] Its effective usage in individuals with severe dengue infection and ALF has been documented.[23] Its effective treatment in a child with fulminant liver failure complicating dengue illness is described in a single case report.[7] According to the review of Tafere et al. (2020), N-acetylcysteine (NAC) could be utilized as a curative treatment for ALF caused by the dengue virus. However, the majority of their evidence comes from adults.[9]

Currently, dengue is recognized as the most significant virus spread by mosquitoes.[13] Although mild to moderate increases in serum aminotransferase levels are typical with dengue infections, acute liver failure (ALF) is a potentially fatal complication for which there is no specific medication and which is generally treated with supportive care.[5] The literature reports a mortality rate from dengue ALF of 0–60%, but the data are too small for statistical significance.[15]

Direct viral damage, a dysfunctional host immune response, or hypoxia damage are thought to be the causes of ALF in dengue infection. Previous research has revealed that the dengue virus may promote the production of Fas ligand on hepatocytes, leading to

immune-mediated hepatocytic damage and cell death.[17,18] The clinical observation of circulatory collapse, a frequent comorbidity with ALF, supports hypoxic damage. While liver enzymes like aspartate transferase (AST) and alanine transferase (ALT) are high after acute dengue virus infection, the level of antioxidants like glutathione peroxidase and glutathione reductase is decreased. This suggests that the dengue virus has caused oxidative stress.[19] Additionally, as explored in a mouse model, the production of inflammatory cytokines, particularly interleukin-22 (IL-22) and interleukin-17 (IL-17), may result in dengue-induced acute liver failure.[20] Interleukin-5 (IL-5) and interleukin-10 (IL-10) were increased later. Tumor necrosis factor (TNF) alpha, interleukin 2 (IL-2), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels are also enhanced in early dengue virus infection.[21] Unknown variables may predispose certain people to developing ALF. Several histologic alterations, such as fatty change, hepatocyte necrosis, hyperplasia, and degeneration of Kupffer cells, Councilman bodies, and mononuclear cell infiltrates at the portal tract, were seen in dengue-induced liver failure.[4] Also, a study found that acetaminophen/ paracetamol overdose can be a significant factor in the development of acute liver failure in dengue patients.[22]

NAC is essential for the treatment of acute liver damage brought on by dengue, presumably through lowering oxidative stress, acting directly against viruses, and improving blood flow to the liver. The potential of NAC to boost antioxidant defense, its free radical scavenging activity, and its vasodilatory activity, which increases blood flow to the liver, may be associated to its mechanism of action in patients who recovered from dengue-induced ALF.[23,24] The antioxidant enzymes glutathione reductase and glutathione peroxidase are decreased during acute dengue infection, according to Chandrasena et al (2019). Thus, the antioxidant action of NAC may be brought on by a rise in plasma levels of antioxidants such glutathione peroxidase and glutathione reductase, which lowers oxidative stress.[19]

Published evidence shown in this systematic review shows that NAC can be a promising treatment to dengue-induced ALF in children. It is also considered safe as none of the four studies observed adverse events in any of their patients. However, three of four of the included studies lack comparison groups and have small number of patients given NAC. The lack of comparison group makes it impossible to estimate an effect size such as risk ratio or odds ratio. On the other hand, small sample size limits the extent to which findings can be generalized in a bigger population. Further investigations, especially of randomized controlled trials with larger sample size, should still be conducted. Furthermore, other basic and advanced

advanced medications, treatments and life-saving interventions to ALF and other dengue-induced complications should be taken into account. Other comorbidities, as well as complications, also play vital role in the prognosis of children diagnosed with severe dengue.

Conclusion and Recommendations

This systematic review shows limited evidence on the effectiveness of N-acetylcysteine in the reversal of liver enzymes among pediatric patients because of the low incidence of dengue induced liver injury seen in observational studies. Given that NAC is reported by all four studies to be accessible, effective, and with no attributable adverse events, its use can be considered. However, clinicians must still be cautioned given the limited available evidence. Large-scale randomized controlled trials are recommended to verify these findings and provide better level of evidence.

Acknowledgement

The primary investigator wishes to extend appreciation and heartfelt thanks to those who played a crucial role in making this study possible. Gratitude is expressed to Dr. Ma. Lucila M. Perez, the technical board adviser, for their patient review of outputs and valuable constructive criticisms that propelled the investigator to complete the study. Special thanks are extended to the Education, Training, and Research Department, as well as the Institutional Research-Ethics Committee, for their continuous guidance and motivation, without which this study would not have progressed.

References

1. Undurraga EA, Edillo FE, Erasmo JN, Alera MT, Yoon IK, Largo FM, Shepard DS. Disease burden of dengue in the Philippines: adjusting for underreporting by comparing active and passive dengue surveillance in Punta Princesa, Cebu City. Am. J. Trop. Med. Hyg. 2017 Apr 4;96(4):887.

2. Dengue and severe dengue [Internet]. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

3. Schaefer TJ, Panda PK, Wolford RW. Dengue fever [Internet]. 2022.

4. Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases. 2015 Feb 16;3(2):125-31. doi: 10.12998/wjcc.v3.i2.125. PMID: 25685758; PMCID: PMC4317605.

5. Senanayake MP, Jayamanne MD, Kankananarachchi I. N-acetylcysteine in children with acute liver failure complicating dengue viral infection. Ceylon Med J. 2013 Jun;58(2):80-2.

6. Dissanayake DMDIB, Gunaratne WMSN, Kumarihamy KWMPP, Kularatne SAM, Kumarasiri PVR. Use of intravenous N-acetylcysteine in acute severe hepatitis due to severe dengue infection: a case series. BMC Infect Dis. 2021 Sep 20;21(1):978. doi: 10.1186/s12879-021-06681-9. PMID: 34544380; PMCID: PMC8454086.

7. Lim G, Lee JH. N-acetylcysteine in children with dengue-associated liver failure: a case report. J Trop Pediatr. 2012 Oct;58(5):409-13. doi: 10.1093/tropej/fmr108. Epub 2011 Dec 23. PMID: 22199018.

8. Laoprasopwattana K, Jundee P, Pruekprasert P, Geater A. Outcome of Severe Dengue Viral Infection-caused Acute Liver Failure in Thai Children. J Trop Pediatr. 2016 Jun;62(3):200-5. doi: 10.1093/tropej/fmv099. Epub 2016 Feb 6. PMID: 26851434.

9. Tafere GG, Wondafrash DZ, Demoz FB. Repurposing of N-Acetylcysteine for the Treatment of Dengue Virus-Induced Acute Liver Failure. Hepat Med. 2020 Nov 3;12:173-178. doi: 10.2147/HMER.S263840. PMID: 33177895; PMCID: PMC7650016.

10. Tan JM, Tan NW, Ong C, Thoon KC, Chong CY. Dengue Fever Associated Liver Failure. Pediatric Infect Dis. 2016;1(31):2573-0282.

11. Medimarketing Inc. Search Drug Information, Interactions, Images, Dosage & Side Effects. MIMS Philippine [Internet]. 2023/ Available from: https://www.mims.com/philippines/

12. Ong EP, Obeles AJT, Ong BAG, Tantengco OAG. Perspectives and lessons from the Philippines' decades-long battle with dengue. Lancet Reg Health West Pac. 2022 Jun 24;24:100505. doi: 10.1016/j.lanwpc.2022.100505. PMID: 35789734; PMCID: PMC9249805.

13. Sharma PK, Kumar M, Sahani A, Goyal R, Aggarwal GK, Kumar V. Severe hepatic-neurological complications of dengue fever in children from a tertiary care center in North India. Age (years). 2016 May 1;5:0-75.

14. Laoprasopwattana K, Khantee P, Saelim K, Geater A. Mortality Rates of Severe Dengue Viral Infection Before and After Implementation of a Revised Guideline for Severe Dengue. Pediatr Infect Dis J. 2022 Mar 1;41(3):211-216. doi: 10.1097/INF.0000000000003411. PMID: 34840312.

15. Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health. 2009 Jan;40(1):47-53. PMID: 19323033.

16. 16. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg. 2006 Jul;100(7):608-14. doi: 10.1016/j.trstmh.2005.10.007. Epub 2006 Feb 17. PMID: 16483623.

17. 17. Marianneau P, Cardona A, Edelman L, Deubel V, Desprès P. Dengue virus replication in human hepatoma cells activates NF-kappaB which in turn induces apoptotic cell death. J Virol. 1997 Apr;71(4):3244-9. doi: 10.1128/JVI.71.4.3244-3249.1997. PMID: 9060688; PMCID: PMC191457.

18. 18. Pagliari C, Quaresma JA, Fernandes ER, Stegun FW, Brasil RA, de Andrade HF Jr, Barros V, Vasconcelos PF, Duarte MI. Immunopathogenesis of dengue hemorrhagic fever: contribution to the study of human liver lesions. J Med Virol. 2014 Jul;86(7):1193-7. doi: 10.1002/jmv.23758. Epub 2013 Sep 23. PMID: 24114877.

19. 19. Chandrasena L, De Silva A, De Mel C, Peiris H, Abesuriya V, De Mel S, Seneviratne S, Bandara S. Glutathione enzymes and liver injury in acute dengue viral infection. J.Biosci. 2019 Oct 18;7(10):61.

20. 20. Guabiraba R, Besnard AG, Marques RE, Maillet I, Fagundes CT, Conceição TM, Rust NM, Charreau S, Paris I, Lecron JC, Renauld JC, Quesniaux V, Da Poian AT, Arruda LB, Souza DG, Ryffel B, Teixeira MM. IL-22 modulates IL-17A production and controls inflammation and tissue damage in experimental dengue infection. Eur J Immunol. 2013 Jun;43(6):1529-44. doi: 10.1002/eji.201243229. Epub 2013 Apr 17. PMID: 23505056.

21. 21. Chia PY, Thein TL, Ong SWX, Lye DC, Leo YS. Severe dengue and liver involvement: an overview and review of the literature. Expert Rev Anti Infect Ther. 2020 Mar;18(3):181-189. doi: 10.1080/14787210.2020.1720652. Epub 2020 Feb 3. PMID: 31971031.

22. 22. World Health Organization. Global strategy for dengue prevention and control 2012-2020.

23. 23. Kumarasena RS, Mananjala Senanayake S, Sivaraman K, de Silva AP, Dassanayake AS, Premaratna R, Wijesiriwardena B, de Silva HJ. Intravenous N-acetylcysteine in dengue-associated acute liver failure. Hepatol Int. 2010 May 28;4(2):533-4. doi: 10.1007/s12072-010-9176-4. PMID: 20827413; PMCID: PMC2900558.

24. 24. Abeysekera RA, Illangasekera U, Jayalath T, Sandeepana AG, Kularatne SA. Successful use of intravenous N-acetylcysteine in dengue haemorrhagic fever with acute liver failure. Ceylon Med J. 2012 Dec;57(4):166-7. doi: 10.4038/cmj.v57i4.5085. PMID: 23292059.