Coagulation abnormalities in Dengue fever infection: A systematic review and meta-analysis

Tiruneh Adane*, Solomon Getawa

Department of Hematology and Immunohematology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

* tirunehadane01@gmail.com

Abstract

Background
Coagulation mechanisms are reported to be affected in dengue illness and evidenced by prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT). The main aim of this systematic review and meta-analysis is to determine the magnitude of coagulation abnormalities among patients with dengue fever infection.

Method
This systematic review and meta-analysis were conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The Joana Briggs Institute (JBI) critical appraisal checklist was used for quality appraisal. STATA version 11 software was used for meta-analysis. The magnitude of coagulation abnormalities among dengue fever patients was determined by using a random-effects model. Subgroup and sensitivity analysis were performed to investigate the possible source of heterogeneity. Egger weighted regression tests were used to check the presence of publication bias among the included articles.

Result
Fifty-two studies with a total of 12,221 dengue fever patients were eligible for meta-analysis in this study. Of which 22, 15, and 26 studies were used to determine the magnitude of prolonged APTT, PT, and thrombocytopenia, respectively. The magnitude of prolonged APTT and PT among patients with dengue fever infection were 42.91% (95% CI: 30.95, 54.87) I² = 99.1% and 16.48% (95% CI: 10.95, 22.01) I² = 97.0%, respectively. Besides, the magnitude of thrombocytopenia among dengue fever patients was 70.29% (95% CI: 62.69, 77.89) I² = 99.3%. The magnitude of prolonged APTT in children and adults were 51.21% (95% CI: 24.54, 77.89) and 49.3% (95% CI: 28.32, 61.45), respectively. Similarly, the overall magnitude of prolonged PT in children and adults were 13.40% (95% CI: 6.09, 20.71) and 18.73% (95% CI: 7.49, 29.96), respectively.
Conclusion

The result of this study showed that there is a high magnitude of prolonged APTT and PT in dengue fever patients. Therefore, screening and early correction of coagulation abnormalities may be helpful to reduce further complications in those patients.

Author summary

Coagulation mechanisms are reported to be affected in dengue illness and evidenced by prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT). The magnitude of prolonged APTT and PT among patients with dengue fever infection were 42.91% (95% CI: 30.95, 54.87) I² = 99.1% and 16.48% (95% CI: 10.95, 22.01) I² = 97.0%, respectively. The magnitude of thrombocytopenia among dengue fever patients was 70.29% (95% CI: 62.69, 77.89) I² = 99.3%. Screening and early correction of coagulation abnormalities may be helpful to reduce further complications in those patients.

Introduction

Dengue is transmitted by the bite of an infected Aedes mosquito. The female Aedes mosquito gets infected with the dengue virus after sucking blood from an infected person during acute febrile illness [1]. Dengue illness is currently the most important mosquito-borne viral disease in the tropical areas of the world [2]. It is caused by one of the four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) and Aedes aegypti is the main vector [3]. The fifth and latest addition to the existing serotypes of dengue viruses is DENV-5 which has been announced in October 2013 [4]. According to estimates of the World Health Organization (WHO), about 50 million cases of Dengue fever (DF) occur annually worldwide and 2.5 billion people live in risk areas [5]. Every year about 50–100 million cases of dengue infection, 500,000 cases of Dengue hemorrhagic fever (DHF) and at least 12,000 deaths occur worldwide; ninety percent of these deaths occur in children less than 15 years of age [6,7].

The DF is classically a self-limiting, nonspecific illness characterized by fever, headache, myalgia, and constitutional symptoms. DHF is a more serious clinical entity. The WHO classifies DHF in four grades (I to IV). The DHF grades I and II represent relatively mild cases without shock, whereas grade III and IV cases are more severe and accompanied by shock [8]. Although DF is a self-limited febrile illness, DHF is characterized by prominent hemorrhagic manifestations with thrombocytopenia, increased vascular permeability, and is associated with a high mortality rate [9]. The primary pathophysiologic abnormality seen in DHF is an acute increase in vascular permeability that leads to plasma leakage into the extravascular compartment [10]. The WHO defines dengue shock syndrome (DSS) as DHF plus signs of circulatory failure manifested by rapid and weak pulse, narrow pulse pressure (≤20 mmHg) or hypotension for age, prolonged capillary refill, cold and clammy skin, and restlessness [1]. Initial infection with a particular serotype (the primary infection) is usually asymptomatic or results in mild disease manifestations. However, subsequent infection (secondary dengue infections) may lead to severe disease which manifests in the form of DHF/DSS [11].

The clinical picture of DF shows abnormal hemostatic activities, which is demonstrated by thrombocytopenia [12]. Thrombocytopenia may occur in DF/DHF as a result of either decreased production (bone marrow suppression) and/or increased peripheral destruction [3]. Platelet destruction may occur as a result of complement activation and also because of
Peripheral sequestration. Hemorrhage may be a consequence of thrombocytopenia and associated platelet dysfunction or disseminated intravascular coagulation (DIC) [13]. Thrombocytopenia is common in DHF and is one of the criteria stipulated by the WHO for the clinical case definition, but it has also been noted in up to 50% of cases of DF [14]. The appearance of IgM antiplatelet antibodies destroying platelets is a predictor for the development of thrombocytopenia. An increased level of platelet-associated IgM during the acute phase of secondary infection was associated with the development of DHF [15].

Initial hemostasis is tightly linked to inflammation. Inflammation-induced during infection generally shifts the hemostatic mechanism toward thrombosis by upregulation of procoagulant factors, down-regulation of anticoagulants, and inhibit fibrinolytic activity [16]. The activated partial thromboplastin time (APTT) and prothrombin time (PT) are screening assays used for the initial assessment of disorders of hemostasis [17]. Coagulation and anticoagulation mechanisms are reported to be affected and evidenced by prolonged APTT, PT, hyperfibrinogenemia, and decreased fibrin monomers [18]. Dysfunction of the damaged liver might be responsible for the decreased synthesis of specific factors in the intrinsic pathway. Increased factor consumption is also associated with APTT prolongation, but in a less significant manner [10]. Dengue viral infection induces the endothelial production of tissue plasminogen activator as well as IL-6. IL-6 can down-regulate the synthesis of coagulation factor XII the first factor to initiate the intrinsic pathway of the coagulation cascade [19].

The main aim of this systematic review and meta-analysis is to determine the magnitude of coagulation abnormalities among dengue fever infection globally. This may help to give insight for the concerned bodies to design appropriate intervention plans and also the early treatment of the patients since dengue fever is one of the neglected diseases.

**Methods**

**Design**

This systematic review and meta-analysis were conducted following the PRISMA guideline [20] (S1 PRISMA Checklist).

**Eligibility criteria**

All studies that reported the magnitude of coagulation abnormalities and also thrombocytopenia among dengue fever patients using the English language and published in the peer-reviewed journal were included. Case-controls, cross-sectional, retrospective cohort, and prospective studies were also included in this study. The study also included articles that reported the magnitude of thrombocytopenia among dengue fever patients without the reports of PT and/or APTT. Studies that reported the coagulation profile of dengue patients in the form of a continuous variable (mean ± standard deviation) were also included in this study. There is no age restriction in the population types included in this study. Review articles, abstracts, editorials, commentaries, and poster presentations were excluded from this study.

**Search strategy**

PubMed, Cochrane Library, Scopus, Google Scholar, and African Journals Online were the major databases used to review all published articles. The search for published studies was not restricted by time, and all published articles up to March 2021 were included in this review. Reference lists of retrieved articles were searched to identify any studies that are not retrieved from electronic databases. The search terms were used separately and in combination using Boolean operators like “OR” or “AND”. The search terms used were coagulation...
abnormalities, coagulation profiles, hematological profiles, partial thromboplastin time, prothrombin time, prolonged APTT, prolonged PT, hemostatic derangement, thrombocytopenia, dengue fever, dengue hemorrhagic fever, and dengue shock syndrome (S1 PubMed Search strategy).

Study selection and quality appraisal

All retrieved articles were imported to EndNote X7 (Thomson Reuters, USA). After excluding duplications, titles and/or abstracts of articles were independently screened by two authors (TA and SG). The authors agreed to settle their argument through discussion. Then, articles that comply with the eligibility criteria and are sufficiently valid for our research question underwent full-text appraisal. JBI critical appraisal checklist for simple prevalence, cohort, and case-control studies was used for quality appraisal using 9, 11, and 10 criteria, respectively. For each question, a score was assigned (0 for ‘not reported or not appropriate’ and 1 for ‘yes’); the scores were summarized across the items to attain a total score that ranged from 0 to 9, 0 to 10, and 0 to 11 for simple prevalence, case-control, and cohort studies, respectively. Studies were then classified as having a low, medium, and high quality based on the awarded points. Articles having high and medium quality were included in the final analysis (S1 Quality Appraisal).

Data extraction

Relevant studies that fulfilled the eligibility criteria were subjected to data extraction and summarized into an excel spreadsheet. Information extracted from the included studies were; the name of the first author, year of study, country, publication year, study design, sample size, the magnitude of thrombocytopenia, prolonged PT, and prolonged APTT (Table 1).

Meta-analysis

STATA version 11 software was used for meta-analysis. Random-effects model was used to determine the magnitude of coagulation abnormalities along with 95% confidence intervals (CIs). The $I^2$ statistics were used to assess the magnitude of heterogeneity from the included articles. The $I^2$ value of 25, 50, and 75 indicates low, medium, and high heterogeneity, respectively [21]. Subgroup and sensitivity analysis were performed to explore the possible source of heterogeneity. Eggers test and funnel plot were used to check the presence of publication bias among the included articles. A P-value $<0.05$ in Egger’s test was considered to be evidence of statistically significant publication bias [22].

Result

Selection of studies

Of the 2450 articles assessed initially for full-text analysis, 42 studies were included in the final meta-analysis. Of the total, 1216 articles were excluded due to duplication and 1175 unrelated articles were excluded by their title and abstract. The remaining 59 full-text articles were assessed for inclusion; of them, 17 full-text articles were excluded with reason. (Fig 1).

Characteristics of included studies

Forty-two studies were included in this study. In total, 23 studies were in India, 8 in Pakistan, 3 in Taiwan, 2 in Brazil, and 2 in Malaysia. In Saudi Arabia, Indonesia, Sri Lanka, and Sudan, 4 articles one from each country have reported coagulation abnormalities in dengue virus infected patients. The number of patients with dengue infection ranges from 24 to 2022, both of them were in India. The total number of study participants in this systematic review and
A meta-analysis was 12,221. With regard to the types of populations, 12 studies were conducted in adults, 13 studies were in children, 14 studies were in all age groups, and the other 3 studies did not explicitly specify their target populations. Ten studies reported the magnitude of both

| Author, year of publication | Year of study | Country | Sample size | Study design | Populations | Prolonged PT | Prolonged APTT | Thrombocytopenia |
|----------------------------|--------------|---------|-------------|-------------|-------------|--------------|----------------|-----------------|
| Pranesh 2020 [13]          | 2018–2019    | India   | 100         | Case-control | Adults      | 49           | 43             | 69              |
| Barbosa et al 2019 [17]    | 2003–2007    | Brazil  | 187         | Retrospective | All age group | 34.2         | 65.8           | -               |
| Hassan et al 2018 [18]     | 2013–2016    | Pakistan | 200         | Observational | Adults      | 13.6         | 21.6           | -               |
| Vijayaraghavan et al 2020 [19] | 2005–2010 | Malaysia | 203         | Retrospective | Children    | -            | 51.85          | 56.4            |
| Kannan et al 2014 [23]     | NR           | India   | 264         | Descriptive  | Children    | -            | 22.3           | -               |
| Balakrishnan et al 2017 [24] | 2013–2014   | India   | 306         | Observational | Adults      | 20.9         | 91.1           | -               |
| Yashaswini et al 2017 [25] | 2016         | India   | 100         | Observational | Adults      | 6            | 38             | -               |
| Kadadavar et al 2019 [26]  | 2016–2018    | India   | 100         | Prospective  | Adults      | -            | 36             | 97              |
| Dhooria et al 2008 [27]    | 2005–2006    | India   | 81          | Retrospective | Children    | 3.7          | -              | 100             |
| Kavitha et al 2020 [28]    | 2016         | India   | 128         | Cross-sectional | All age group | -            | 86.1           | 89              |
| Kalori et al 2011 [29]     | 2010         | India   | 356         | Cross-sectional | All age group | -            | 24             | 89              |
| Hamza et al 2019 [30]      | 2017         | India   | 170         | Prospective  | Adults      | -            | 64.7           | 25.9            |
| Jameel et al 2012 [31]     | 2010         | Pakistan | 364         | Cross-sectional | NR          | 24           | 25             | -               |
| Ali et al 2007 [32]        | 2001–2006    | Pakistan | 210         | Retrospective | All age group | 2.5          | 16.7           | 77.1            |
| Khalil et al 2014 [33]     | 2008–2010    | Pakistan | 532         | Retrospective | Adults      | 12           | 42.3           | 98.12           |
| Mallhi et al 2017 [34]     | 2008–2013    | Malaysia | 667         | Retrospective | Adults      | 33.3         | 23.8           | 59.2            |
| Ayub et al 2006 [35]       | 2004–2005    | Saudi Arabia | 80         | Prospective  | All age group | 0            | 25.64          | 58.97           |
| Budastra et al 2009 [36]   | 2007         | Indonesia | 131         | Prospective  | Children    | 15.26        | 16.03          | -               |
| Liu et al 2013 [37]        | 2002         | Taiwan  | 100         | Observation  | Adults      | 1.5          | 89.7           | 100             |
| Kulasinghe et al 2016 [38] | 2013         | Sri Lanka | 384         | Prospective  | Children    | -            | 67             | -               |
| Bashir et al 2015 [39]     | 2013–2014    | Sudan   | 334         | Prospective  | All age group | 9            | 12.6           | 83.5            |
| Khan et al 2020 [40]       | 2018–2019    | Pakistan | 310         | Cross-sectional | NR          | 6.3          | 25.26          | 48              |
| Shah et al 2005 [41]       | 2004         | India   | 69          | Prospective  | Children    | 24.1         | 55.9           | 50              |
| Ghalige et al 2014 [42]    | 2010–2012    | India   | 100         | Observation  | Children    | 15.5 ±1.3    | 36.9 ±2.4      | 43              |
| Selvam et al 2015 [43]     | 2015         | India   | 300         | Prospective  | Children    | -            | -              | 92              |
| Khan et al 2014 [44]       | 2011–2012    | Pakistan | 250         | Retrospective | All age group | -            | -              | 65.2            |
| Tulara et al 2019 [45]     | 2017         | India   | 112         | Prospective  | Adults      | -            | -              | 97              |
| Kumari et al 2020 [46]     | NR           | India   | 210         | Observational | Children    | -            | -              | 99.52           |
| Tong et al 2007 [47]       | 2003         | India   | 24          | Prospective  | All age group | -            | -              | 87.5            |
| Castilho et al 2020 [48]   | 2014         | Brazil  | 387         | Retrospective | All age group | -            | -              | 40.3            |
| Rai et al 2019 [49]        | 2016–2018    | India   | 2022        | Prospective  | All age group | -            | -              | 62.6            |
| Tewari et al 2018 [50]     | 2013         | India   | 443         | Observation  | All age group | -            | -              | 67              |
| Chairulfatha et al 2003 [51]| 1995–1996    | India   | 1300        | Retrospective | All age group | -            | -              | 58              |
| Khan et al 2014 [52]       | 2011–2012    | Pakistan | 107         | Retrospective | All age group | -            | -              | 71              |
| Patel et al 2020 [53]      | NR           | India   | 80          | Descriptive  | Adults      | -            | -              | 85              |
| Almas et al 2010 [54]      | 2007         | Pakistan | 699         | Cross-sectional | Adults      | 13.02±4.62   | 36.50±12.28   | -               |
| Prabhavathi et al 2017 [55]| NR           | India   | 100         | Prospective  | Children    | 12.4 ± 1.1   | 26.7 ± 4.1    | -               |
| Hsieh et al 2016 [56]      | 2015         | Taiwan  | 75          | Retrospective | Adults      | -            | 44.9±11.1     | -               |
| Kumar et al 2017 [57]      | 2015         | India   | 306         | Descriptive  | Children    | 19±3.7       | 46±7          | -               |
| Ho et al 2013 [58]         | 2007         | Taiwan  | 100         | Retrospective | Children    | -            | 40 ± 45       | -               |
| Bandaru et al 2019 [59]    | 2019         | India   | 105         | Prospective  | Children    | 16.8 ± 7.9   | 48.3 ± 21.2   | -               |
| Vinoj M 2019 [60]          | 2019         | India   | 100         | Prospective  | All age group | -            | 45.22 ±7.08   | -               |

NR: not reported/appropriate

https://doi.org/10.1371/journal.pntd.0009666.t001
prolonged APTT, prolonged PT, and thrombocytopenia while 20 studies reported the magnitude of both prolonged APTT and PT among dengue fever patients. Twenty-six studies reported the magnitude of thrombocytopenia without the reports of PT and/or APTT among dengue fever patients (Table 1).
The magnitude of prolonged APTT and PT in dengue fever infection

Using 22 studies conducted in different countries of the world, the magnitude of prolonged APTT in patients with dengue fever was 42.91% (95% CI: 30.95, 54.87) $I^2 = 99.1%$. The minimum and maximum magnitude of prolonged APTT were 12.6% [39] and 91.10% [24] in Indonesia and India, respectively. In this review, 15 studies were included to determine the magnitude of prolonged PT among dengue fever patients. The minimum and maximum time prolongation of PT were 1.5% [37] and 49% [13] in Taiwan and India, respectively. Accordingly, the overall magnitude of prolonged PT was 16.48% (95% CI: 10.95, 22.01) $I^2 = 97.0%$ (Fig 2).

Nine studies [41,42,54–60] were used to summarize prolonged APTT in the form of mean±SD in patients with dengue fever. Accordingly, the summarized mean of APTT in the included studies was 41.65 ±7.39 (95% CI: 41.29, 42.01). Besides, using 6 studies [41,42,54,55,57,59], the mean PT value was 15.17±2.47 (95% CI: 15.04, 15.30).

Magnitude of thrombocytopenia in dengue fever patients

A total of 26 studies were evaluated to determine the overall magnitude of thrombocytopenia in dengue fever patients. The lowest and highest magnitude of thrombocytopenia among the included studies was 25.9% in Saudi Arabia [30] and 97.00% [33] in India, respectively. The overall magnitude of thrombocytopenia among dengue fever patients was 70.29% (95% CI: 62.69, 77.89) $I^2 = 99.3%$ (Fig 3).

---

**Fig 2.** Forest plot displaying A. The magnitude of prolonged APTT among dengue fever patients B. The magnitude of prolonged PT among dengue fever patients.

https://doi.org/10.1371/journal.pntd.0009666.g002
Fig 3. Forest plot displaying the magnitude of thrombocytopenia among dengue fever patients.

https://doi.org/10.1371/journal.pntd.0009666.g003
Sub-group analysis based on target populations

To investigate the possible source of heterogeneity, we have done a sub-group analysis using the target populations of the included studies (children, adults, all age groups, and age group not specified). The magnitude of prolonged APTT in children, adults, all age groups, and age group not specified (NR) was 51.21% (95% CI: 24.54, 77.89), 44.89% (95% CI: 28.32, 61.45), 38.44% (95% CI: 11.34, 61.54), and 23.81% (95% CI: 20.48, 27.14) respectively. Similarly, the pooled time prolongation of PT in children, adults, and all age groups was 13.40% (95% CI: 6.09, 20.71), 18.73% (95% CI: 7.49, 29.96), and 14.70% (95% CI: 2.27, 27.13), respectively. The $I^2$ test indicated high heterogeneity both in prolonged APTT ($I^2 = 99.1\%, P<0.001$) and prolonged PT ($I^2 = 97.0\%, P<0.001$) (Fig 4).

Publication bias

The presence of publication bias was determined statistically by the Eggers test and visually by funnel plot. The result showed that there is no significant publication bias among studies included to determine the magnitude of prolonged APTT (p-value = 0.883). However, there is significant publication bias among the included studies to determine the magnitude of prolonged PT (p-value = 0.001) (Fig 5).

Trim and fill analysis

Since we have detected significant publication bias, trim and fill analysis was done to overcome the impact of the small-study effect. Six additional studies were filled to the model, and the

Fig 4. A Sub-group analysis of prolonged APTT based on age distribution. B. Sub-group analysis of prolonged PT based on age distribution.

https://doi.org/10.1371/journal.pntd.0009666.g004
Overall magnitude of prolonged PT in the random-effect model were found to be 6.09% (95% CI: -0.64, 12.82).

Sensitivity analysis
Since there is a high level of heterogeneity in the included studies, a sensitivity analysis was done to assess the effect of each study on the overall result. However, the result of the analysis revealed that the individual studies don’t affect the overall magnitude of coagulation abnormalities as indicated in Tables 2 and 3.

Meta-regression
We have done meta-regression by considering the continuous covariate year of publication. The result of the meta-regression showed that the overall magnitude of prolonged PT and APTT among dengue fever patients was not associated with year of publication (Table 4).

Discussion
A total of 42 studies were included in this systematic review and meta-analysis. Accordingly, the magnitude of prolonged APTT and PT was 42.91% (95% CI: 30.95, 54.87) \( I^2 = 99.1\% \) and 16.48% (95% CI: 10.95, 22.01) \( I^2 = 97.0\% \), respectively. We have used 9 studies that reported prolonged APTT in the form of mean ± SD. Accordingly, the mean APTT in the included studies was 41.65 ± 7.39 (95% CI: 41.29, 42.01). Besides, using 6 studies, the mean PT value was 15.17 ± 2.47 (95% CI: 15.04, 15.30).

Dengue infection is characterized by increased vascular permeability and abnormal hemostasis [12]. Platelet function is also abnormal in dengue infections [61]. Coagulopathy is multifactorial and may be due to low platelets, deranged PT, APTT, and hepatitis [33]. Damage to liver cells decreases the coagulation factor synthesis and this, in turn, can alter the PT and APTT systems [24]. The APTT and PT are indicators of the intrinsic and extrinsic pathways of the coagulation system. Prolongation of PT and APTT might be caused either by the down-regulation of synthesis of specific factors or by an increase in consumption of specific factors.

Fig 5. Funnel plot of included studies A. on the magnitude of APTT dengue fever patients B. on the magnitude of PT dengue fever patients.

https://doi.org/10.1371/journal.pntd.0009666.g005
The non-structural protein 1 (NS1) of the dengue virus can bind both to thrombin and prothrombin. Binding to thrombin will not make any changes whereas prothrombin activation is inhibited. This can explain changes in APTT occur early before antibodies are formed [62]. Coagulopathy as indicated by prolongation of APTT shows an abnormality in the intrinsic pathway of coagulation which lasts only for few days during the disease course [23]. APTT prolongation in the DF patients is caused by a lack of intrinsic pathway probably due to impaired synthesis of coagulation factor [10]. Reductions in the levels of specific coagulation factors are also reported during dengue infection [19].

### Table 2. Sensitivity analysis to estimate the effect each study on the magnitude of prolonged APTT among patients with dengue virus infection.

| Study omitted                  | Point Estimate | 95% Conf. Interval | Heterogeneity |
|-------------------------------|----------------|--------------------|---------------|
|                               |                | Lower              | Upper         | I²   | P-Value |
| Pranesh 2020 [13]             | 42.90          | 30.58              | 55.23         | 99.2%| <0.001  |
| Barbosa et al 2019 [17]       | 41.82          | 29.52              | 54.12         | 99.2%| <0.001  |
| Hassan et al 2018 [18]        | 43.93          | 31.56              | 56.30         | 99.2%| <0.001  |
| Vijayaraghavan et al 2020 [19]| 42.48          | 30.08              | 54.88         | 99.2%| <0.001  |
| Balakrishnan et al 2017 [24]  | 40.56          | 30.71              | 50.41         | 98.5%| <0.001  |
| Kadadavar et al 2019 [26]     | 43.23          | 30.90              | 55.26         | 99.2%| <0.001  |
| Kavitha et al 2020 [28]       | 40.84          | 28.94              | 52.75         | 99.1%| <0.001  |
| Kalori et al 2011 [29]        | 43.82          | 31.32              | 56.31         | 99.1%| <0.001  |
| Hansa et al 2019 [30]         | 41.87          | 29.57              | 54.18         | 99.2%| <0.001  |
| Jameel et al 2012 [31]        | 43.77          | 31.26              | 56.28         | 99.1%| <0.001  |
| Ali et al 2007 [32]           | 44.16          | 31.85              | 56.47         | 99.1%| <0.001  |
| Khalil et al 2014 [33]        | 42.94          | 30.22              | 55.66         | 92.2%| <0.001  |
| Mallhi et al 2017 [34]        | 44.83          | 31.17              | 56.48         | 99.1%| <0.001  |
| Budastra et al 2009 [36]      | 44.19          | 31.91              | 56.47         | 99.1%| <0.001  |
| Liu et al 2013 [37]           | 40.67          | 28.87              | 52.47         | 99.1%| <0.001  |
| Bashir et al 2015 [39]        | 44.37          | 32.26              | 56.47         | 99.1%| <0.001  |
| Shah et al 2005 [41]          | 42.31          | 30.03              | 54.59         | 99.2%| <0.001  |
| Khan et al 2020 [52]          | 43.75          | 31.28              | 56.23         | 99.2%| <0.001  |
| **Combined**                  | 42.91          | 30.95              | 54.87         | 99.1%| <0.001  |

### Table 3. Sensitivity analysis of the included studies to estimate the magnitude of prolonged PT among patients with dengue virus infection.

| Study omitted                  | Point Estimate | 95% Conf. Interval | Heterogeneity |
|-------------------------------|----------------|--------------------|---------------|
|                               |                | Lower              | Upper         | I²   | P-Value |
| Pranesh 2020 [13]             | 14.45          | 9.10               | 19.81         | 96.8%| <0.001  |
| Barbosa et al 2019 [17]       | 15.23          | 9.75               | 20.71         | 96.9%| <0.001  |
| Hassan et al 2018 [18]        | 16.71          | 10.86              | 22.56         | 97.5%| <0.001  |
| Dhoooria et al 2008 [22]      | 17.44          | 11.60              | 23.38         | 97.1%| <0.001  |
| Jameel et al 2012 [31]        | 15.92          | 10.28              | 21.55         | 96.9%| <0.001  |
| Ali et al 2007 [32]           | 17.56          | 11.66              | 23.47         | 96.7%| <0.001  |
| Khalil et al 2014 [33]        | 16.88          | 10.78              | 22.98         | 97.2%| <0.001  |
| Mallhi et al 2017 [34]        | 15.00          | 10.22              | 19.78         | 95.6%| <0.001  |
| Budastra et al 2009 [36]      | 16.58          | 10.79              | 22.37         | 97.2%| <0.001  |
| Liu et al 2013 [37]           | 17.62          | 11.81              | 23.44         | 96.8%| <0.001  |
| Bashir et al 2015 [39]        | 17.09          | 11.05              | 23.13         | 97.2%| <0.001  |
| Shah et al 2005 [41]          | 16.02          | 10.33              | 21.70         | 97.2%| <0.001  |
| Khan et al 2020 [52]          | 17.30          | 11.23              | 23.37         | 97.1%| <0.001  |
| **Combined**                  | 16.48          | 10.95              | 21.01         | 97.0%| <0.001  |
factors such as II, V, VII, VIII, IX, X, antithrombin, and alpha-2 antiplasmin have been reported in DHF patients [18]. The IL-6 plays its role in down-regulating the synthesis of factor XII, the first factor to initiate the intrinsic pathway of coagulation [23].

The other laboratory abnormality determined in this study was the magnitude of thrombocytopenia among dengue fever patients. Twenty-six studies were included to determine the pooled prevalence of thrombocytopenia in dengue fever patients. Accordingly, 70.29% (95% CI: 62.69, 77.89) of those patients had thrombocytopenia. Platelet counts begin to fall during the febrile stage and reach their nadir during the toxic stage [63]. The development of thrombocytopenia in dengue fever infection might be due to depression of bone marrow observed in the acute stage of dengue virus infection. Other explanations are direct infection of the megakaryocytes by virus leading to increased destruction of the platelets or the presence of antibodies directed against the platelets [35]. The third mechanism is increased platelet consumption from the interaction between platelets and endothelial cells infected with dengue virus was demonstrated in vitro and suggested that some dengue-injured endothelial cells might promote platelet adherence and lysis [64].

The subgroup analysis in this review showed that children experienced prolonged APTT than other age groups. This might be explained that dengue infection was thought to be a disease that mostly affected children. DHF has been described as a disease that almost exclusively affects children age <16 years [65]. A study conducted by Hamond et al showed that infants and children 4–6 years of age were significantly more likely than adults to develop DHF/DSS or manifestations of severe clinical illness [66]. The presence of shock and hemorrhagic manifestations during infancy can be attributed to passively transferred circulating antibodies from the mother [67]. However, some studies have reported that the age distribution of this disease has shifted to older age groups [68]. The major burden of disease in infants and children 5 to 9 years of age can be expected in a country that has been endemic for dengue for a long period of time. However, countries with a shorter or non-endemic history of dengue report cases principally in the adolescent and adult population [66]. In this study, in the contrary to the result of prolonged APTT, the results of the prolonged PT was higher in adults than in the other age groups.

This study had some limitations to be considered. The study did not explore potential factors contributing to prolonged APTT, prolonged PT, and also thrombocytopenia in dengue fever patients. Besides this study didn’t summarize factor deficiencies in dengue fever patients. We also included articles published in the English language only.

### Conclusion

The result of this study showed that there is high magnitude of prolonged APTT and PT in dengue fever patients. Therefore, screening and early correction of coagulation abnormalities may be helpful to reduce further complications in those patients.

### Supporting information

S1 PRISMA Checklist.

(DOCX)
Acknowledgments
We are very grateful to all the authors of the included studies in this systematic review and meta-analysis.

Author Contributions
Conceptualization: Tiruneh Adane, Solomon Getawa.
Data curation: Tiruneh Adane.
Formal analysis: Tiruneh Adane.
Investigation: Tiruneh Adane.
Methodology: Tiruneh Adane, Solomon Getawa.
Project administration: Solomon Getawa.
Resources: Solomon Getawa.
Software: Tiruneh Adane, Solomon Getawa.
Supervision: Tiruneh Adane.
Validation: Tiruneh Adane, Solomon Getawa.
Visualization: Solomon Getawa.
Writing – original draft: Tiruneh Adane.
Writing – review & editing: Tiruneh Adane, Solomon Getawa.

References
1. Singhi S, Kissoon N, Bansal A. Dengue and dengue hemorrhagic fever: management issues in an intensive care unit. Jornal de pediatria. 2007; 83(2):S22–S35.
2. Srichaikul T, Nimmannitya S. Haematology in dengue and dengue haemorrhagic fever. Best Practice & Research Clinical Haematology. 2000; 13(2):261–76. https://doi.org/10.1053/beha.2000.0073 PMID: 10942625
3. Mourão M, Lacerda M, Macedo V, Mourão M, Lacerda M, Macedo V, et al. Thrombocytopenia in patients with dengue virus infection in the Brazilian Amazon. Platelets. 2007; 18(8):605–12. https://doi.org/10.1080/0953710701426604 PMID: 18041652
4. Mustafa M, Rasotgi V, Jain S, Gupta V. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. Medical journal armed forces India. 2015; 71(1):67–70. https://doi.org/10.1016/j.mjafi.2014.09.011 PMID: 25609867
5. Organization WH, Research SPI, Diseases TIT, Diseases WHODoCoNT, Epidemic WHO, Alert P. Dengue: guidelines for diagnosis, treatment, prevention and control: World Health Organization; 2009.
6. Organization WH. Strengthening implementation of the global strategy for dengue fever/dengue haemorrhagic fever prevention and control. Report of the Informal Consultation, 18–20 October 1999, WHO HQ, Geneva, Switzerland. Strengthening implementation of the global strategy for dengue fever/dengue haemorrhagic fever prevention and control Report of the Informal Consultation, 18–20 October 1999, WHO HQ, Geneva, Switzerland. 2000.
7. Organization WH. Scientific Working group on dengue meeting report, Geneva, Switzerland. Geneva: WHO. 2000.

8. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. Clinical microbiology reviews. 2009; 22(4):564–81. https://doi.org/10.1128/CMR.00035-09 PMID: 19822889

9. NIMMANNITYA S. Clinical spectrum and management of dengue haemorrhagic fever. Southeast Asian Journal of Tropical Medicine and Public Health. 1997; 18(3):392–7. PMID: 3433169

10. Rachman A, Rinaldi I. Coagulopathy in dengue infection and the role of interleukin-6. Southeast Asian Journal of Tropical Medicine and Public Health. 2006; 38(2):105–8. PMID: 16799214

11. Malavige G, Fernando N, Ogg G. Pathogenesis of dengue viral infections. Sri Lankan Journal of Infectious Diseases. 2011; 1(1). https://doi.org/10.1371/journal.pone.0020581 PMID: 21694773

12. Nimmannitya S, editor. Dengue hemorrhagic fever: disorders of hemostasis. Bangkok, Thailand: Proceedings of the International Congress of Hemostasis, Asia-Pacific Division; 1999: Citeseer.

13. Pranesh S. A Study of Activated Partial Thromboplastin Time and Prothrombin Time as Predictors for Impaired Coagulation among Patients with Dengue Virus Infection in Coimbatore Medical College & Hospital, Coimbatore: Coimbatore Medical College, Coimbatore; 2020.

14. Organization WH. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. World Health Organization; 1997.

15. Lei H-Y, Yeh T-M, Liu H-S, Lin Y-S, Chen S-H, Liu C-C. Immunopathogenesis of dengue virus infection. Journal of biomedical science. 2001; 8(5):377–88. https://doi.org/10.1007/BF02255946 PMID: 11549879

16. Chuang Y-C, Lin Y-S, Liu C-C, Liu H-S, Liao S-H, Shi M-D, et al. Factors contributing to the disturbance of coagulation and fibrinolysis in dengue virus infection. Journal of the Formosan Medical Association. 2013; 112(1):12–7. https://doi.org/10.1016/j.jfma.2012.10.013 PMID: 23332424

17. Barbosa ACN, Montalvão SAL, Barbosa KGN, Colella MP, Annichino-Bizzacchi JM, Ozelo MC, et al. Prolonged APTT of unknown etiology: A systematic evaluation of causes and laboratory resource use in an outpatient hemostasis academic unit. Research and practice in thrombosis and haemostasis. 2019; 3(4):749–57. https://doi.org/10.1002/rth2.12252 PMID: 31624795

18. Hassan J, Borhany M, Abid M, Zaidi U, Fatima N, Shamsi T. Coagulation abnormalities in dengue and dengue haemorrhagic fever patients. Transfusion Medicine. 2020; 30(1):46–50. https://doi.org/10.1111/tme.12658 PMID: 31854052

19. Vijayaraghavan YT, Wei F, Paille H. Predictors of Dengue Shock Syndrome: APTT Elevation as a Risk Factor in Children with Dengue Fever. J Infect Dis Epidemiol. 2020; 1(1). https://doi.org/10.1186/s11539-018-0119-1

20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015; 4(1):1–9. https://doi.org/10.1186/s40647-015-0051-7 PMID: 25554246

21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002; 21(11):1539–58. https://doi.org/10.1002/sim.1186 PMID: 12111919

22. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629 PMID: 9310563

23. Kannan A, Narayanan KS, Sasikumar S, Philipose J, Surendran SA. Coagulopathy in dengue fever patients. Int J Res Med Sci. 2014; 2(3):1070–2.

24. Vijayakumar Balakrishnan SL, Lalitha Kailas. The coagulation profile of children admitted with dengue fever and correlation with clinical severity. International Journal of Contemporary Pediatrics. 2017; 4(6):5. http://dx.doi.org/10.18203/2349-3291.ijcpp20174741.

25. Priya Yashaswini L. A study of hematological parameters and requirement of platelet transfusion in dengue fever. Int J Adv Med. 2017; 4(6):1668.

26. Kadadavar SS, Lokapur V, Nadig D, Prabhu M, Masur D. Hematological parameters in dengue fever: A study in tertiary care hospital. Indian Journal of Pathology and Oncology. 2020; 7(2):218–22.

27. Dhoooria GS, Bhat D, Bains HS. Clinical profile and outcome in children of dengue hemorrhagic fever in North India. 2008. https://doi.org/10.4103/0255-0857.40539 PMID: 18445961

28. Kavitha R, Clarin JD. A Study of Incidence and Significance of Section Coagulopathy among Dengue Patients Admitted in a Tertiary Care Hospital at Tirunelveli, Tamil Nadu, India. 2020.

29. Karoli R, Fatima J, Siddiqi Z, Kazmi KI, Sultania AR. Clinical profile of dengue infection at a teaching hospital in North India. The Journal of Infection in Developing Countries. 2012; 6(07):551–4.

30. Hamsabalan N, Hamsa B. T, SSV, Prabhakar K., Raveesh A., Manoj A. G. Significance of APTT as early predictor of bleeding in comparison thrombocytopenia in dengue virus infection. International Journal of Research in Medical Sciences[January2019]Vol 7 Issue 1Page 67International Journal of Research in Medical Sciences. 2019; 7(1):4. http://dx.doi.org/10.18203/2320-6012.ijrms20185094.
31. Jameel T, Mehmood K, Muttappa G, Choudhry N, Afzal N, Paul RF. Changing haematological parameters in dengue viral infections. Journal of Ayub Medical College Abbottabad. 2012; 24(1):3–6. PMID: 23855082

32. Ali N, Usman M, Syed N, Khurshid M. Haemorrhagic manifestations and utility of haematological parameters in dengue fever: a tertiary care centre experience at Karachi. Scandinavian journal of infectious diseases. 2007; 39(11–12):1025–8. https://doi.org/10.1080/00365540701411492 PMID: 17852892

33. Khalil MAM, Tan J, Khalil MAU, Awan S, Rangasami M. Predictors of hospital stay and mortality in dengue virus infection-experience from Aga Khan University Hospital Pakistan. BMC research notes. 2014; 7(1):1–7.

34. Mallhi TH, Khan AH, Sarriff A, Adnan AS, Khan YH. Determinants of mortality and prolonged hospital stay among dengue patients attending tertiary care hospital: a cross-sectional retrospective analysis. BMJ open. 2017; 7(7):e016805. https://doi.org/10.1136/bmjopen-2017-016805 PMID: 28698348

35. Ayyub M, Khazindar AM, Lubbad EH, Barlas S, Alfi AY, Al-Ukayli S. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia. Journal of Ayub Medical College Abbottabad. 2006; 18(2):9–13.

36. Budastra I, Arhana B, Mudita I. Plasma prothrombin time and activated partial thromboplastin time as predictors of bleeding manifestations during dengue hemorrhagic fever. Paediatrica Indonesiana. 2009; 49(2):69–74.

37. Liu J-W, Lee I-K, Wang L, Chen R-F, Yang KD. The usefulness of clinical-practice-based laboratory data in facilitating the diagnosis of dengue illness. BioMed research international. 2013; 2013.

38. Kulasinghe S, Ediriweera R, Kumara P. Association of abnormal coagulation tests with dengue virus infection and their significance as early predictors of fluid leakage and bleeding. Sri Lanka Journal of Child Health. 2016; 45(3).

39. Mohammed BAB. Deranged liver among Sudanese patients with dengue virus infection in Port Sudan Teaching Hospital. Sudan Journal of Medical Sciences. 2017; 12(3):187–97.

40. Khan S, Baki MA, Ahmed T, Mollah MAH. Clinical and laboratory profile of dengue fever in hospitalized children in a tertiary care hospital in Bangladesh. BMJ open. 2020; 10(3):200–3.

41. Shah I, Katira B. Clinical and Laboratory Abnormalities due to Dengue in Hospitalized Children in Mumbai in 2004. 2005.

42. Ghalige SS, Reddy CU, Prakash S, Aradhya GH. Bleeding risk in Dengue fever: A clinico-laboratory profile study. RGUHS Journal of Medical Sciences. 2014; 4(4):189–92.

43. Selvan T, Souza JLD, Giridhar NS, Kumar M. Prevalence and severity of Thrombocytopenia in Dengue fever in children. Scholars journal of Applied Medical Sciences (SJAMS). 2015; 3(5D):2068–70.

44. Khan MU, Rehman R, Gulfraz M, Latif W. Incidence of thrombocytopenia in seropositive dengue patients. International Journal of Medicine and Medical Sciences. 2014; 6(4):113–6.

45. Tulara NK. Dengue fever and thrombocytopenia—A prospective Observational Study at Tertiary Care Centre. Eastern Journal of Medical Sciences. 2019;45–8.

46. Kumari S, Makwana M, Mourya HK, Mitharwal R, Ram S, Meena A, et al. An observational study to determine the incidence and the clinico-epidemiologic profile of dengue fever in paediatric age group presenting to a tertiary care centre in Western Rajasthan, India. 2020.

47. Tong S, Aziz N, Chin G. Predictive value of thrombocytopenia in the diagnosis of dengue infection in outpatient settings. The Medical journal of Malaysia. 2007; 62(5):390–3. PMID: 18705473

48. Castilho BM, Silva MT, Freitas AR, Fulone I, Lopes LC. Factors associated with thrombocytopenia in patients with dengue fever: a retrospective cohort study. BMJ open. 2020; 10(9):e035120. https://doi.org/10.1136/bmjopen-2019-035120 PMID: 32928847

49. Rai A, Azad S, Nautiyal S, Acharya S. Correlation between hematological and serological parameters in dengue patients-an analysis of 2022 cases.

50. Tewari K, Tewari VV, Mehta R. Clinical and hematological profile of patients with dengue fever at a tertiary care hospital—an observational study. Mediterranean journal of hematology and infectious diseases. 2018; 10(1).

51. Chairulfa AH, Setiabudi D, Agoes R, Colebunders R. Thrombocytopenia and Platelet Trasnusions in Dengue Haemorrhagic Fever and Dengue Shock Syndrome. 2003.

52. Khan DM, Kuppusamy K, Sumathi S, Mrinalini V. Evaluation of thrombocytopenia in dengue infection along with seasonal variation in rural Melmaruvathan. Journal of clinical and diagnostic research: JCDR. 2014; 8(1):39. https://doi.org/10.7860/JCDR/2014/6739.3914 PMID: 24596719

53. Patel MK, Patel HJ. Assessment of clinical and hematological profile in dengue fever. International Journal of Advances in Medicine. 2020; 7(9):1418.
54. Almas A, Parkash O, Akhter J. Clinical factors associated with mortality in dengue infection at a tertiary care center. Southeast Asian J Trop Med Public Health. 2010; 41(2):333–40. PMID: 20578516

55. Prabhavathi R, Madhusudan S, Suman M, Govindaraj M, Puttaswamy M. Study of clinical and laboratory predictive markers of dengue fever and severe dengue in children. J Pediatr Res. 2017; 4(6):397–404.

56. Hsieh C-C, Cia C-T, Lee J-C, Sung J-M, Lee N-Y, Chen P-L, et al. A cohort study of adult patients with severe dengue in Taiwanese intensive care units: the elderly and APTT prolongation matter for prognosis. PLoS neglected tropical diseases. 2017; 11(1):e0005270. https://doi.org/10.1371/journal.pntd.0005270 PMID: 28060934

57. Kumar BV, Simna L, Kalhana D, Kailas L. Clinical profile and outcome of children admitted with dengue fever in a tertiary care hospital in South India. Indian Journal of Child Health. 2018; 5(1):32–7.

58. Ho T-S, Wang S-M, Lin Y-S, Liu C-C. Clinical and laboratory predictive markers of acute dengue infection. Journal of biomedical science. 2013; 20(1):1–8. https://doi.org/10.1186/1423-0127-20-75 PMID: 24138072

59. Bandaru AK, Vanumuthu DS. Correlation of liver indices with thrombocytopenia in dengue infected children.

60. Vinoj M. Association of Abnormal Coagulation Profile and Liver Enzymes with Dengue Infection and Their Significance as Predictors of Assessing Severity of Disease: Madurai Medical College, Madurai; 2019.

61. Wills BA, Oragui EE, Stephens AC, Daramola OA, Dung NM, Loan HT, et al. Coagulation abnormalities in dengue hemorrhagic fever: serial investigations in 167 Vietnamese children with dengue shock syndrome. Clinical infectious diseases. 2002; 35(3):277–85. https://doi.org/10.1086/341410 PMID: 12115093

62. Isarangkura P, Pongpanich B, Pintadit P, Phanichyangkarn P, Valyasevi A. Hemostatic derangement in dengue haemorrhagic fever. The Southeast Asian journal of tropical medicine and public health. 1987; 18(3):331–9. PMID: 3433165

63. Chuansumrit A, Chaiyaratana W. Hemostatic derangement in dengue hemorrhagic fever. Thrombosis research. 2014; 133(1):10–6. https://doi.org/10.1016/j.thromres.2013.09.028 PMID: 24120237

64. Funahara Y, Ogawa K, Fujita N, Okuno Y. Three possible triggers to induce thrombocytopenia in dengue virus infection. The Southeast Asian journal of tropical medicine and public health. 1987; 18(3):351–5. PMID: 3433166

65. Hanafusa S, Chanyasanha C, Sujirarat D, Khuankhamnathid I, Yaguchi A, Suzuki T. Clinical features and differences between child and adult dengue infections in Rayong Province, southeast Thailand. 2008. PMID: 18564710

66. Hammond SN, Balmaseda A, Perez L, Tellez Y, Saborío SI, Mercado JC, et al. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. The American journal of tropical medicine and hygiene. 2005; 73(6):1063–70. PMID: 16354813

67. Aggarwal A, Chandra J, Aneja S, Patwari A, Dutta A. An epidemic of dengue hemorrhagic fever and dengue shock syndrome in children in Delhi. Indian pediatrics. 1998; 35:727–32. PMID: 10216566

68. García-Rivera EJ, Rigau-Pérez JG. Dengue severity in the elderly in Puerto Rico. Revista Panamericana de Salud Pública. 2003; 13:362–8. https://doi.org/10.1590/s1020-49892003000500004 PMID: 12880516