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Systematic review on factors of mortality among dengue patients in Malaysia

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***Abstract*---**Introduction: Malaysia has a high concentration of dengue cases. Even though the case fatality rate is low among dengue patients, identification of the risk factors of dengue mortality helps in the management of these patients. Findings from previous studies were inconclusive, thus, we systematically review studies to identify the factors of mortality among dengue patients in Malaysia. Methods: Three main search engines such as PubMed, ScienceDirect and EBSCO were used to screen the articles. This systematic review follows PRISMA guidelines. Results: The initial search yielded a total of 523 articles to be reviewed. However, after screening, four articles were left with all of them being quantitative studies. From the four studies accepted, thirty-six factors were identified. The factors include age, gender, nausea, vomiting, bleeding, lethargy, body ache, abdominal pain, retro-orbital pain, dysuria, shock, pleural effusion, ascites, prolonged Prothrombin Time (PT), Haematocrit (HCT)>20%, Serum pH <7.35, Serum ferritin >10,000 ni/mL, serum creatinine, serum lactate >2, white blood cell (WBC) count, insulin dependant

diabetes, ischemic cardiovascular disease and progressive renal disease. Conclusions: To conclude, age and bleeding were found as the most important health risk for Dengue patients and poses a great liability towards mortality among patients infected with dengue in Malaysia.

Keywords---Dengue, Factors, Mortality, Haemorrhagic Fever, Malaysia.

Introduction

Dengue Fever is a viral infection of vector origin. There are currently 4 serotypes known to cause the infection which is Dengue Virus which are further divided into several serological subtypes (DENV 1-4). It is commonly disseminated by the mosquito from Aedes species, especially the female Aedes aegypti Culicidae which is classified as the predominant carrier of serological types of DENV. The mosquito habitat is usually in urban areas where it breeds inside containers that contain water. The feeding time for this mosquito species is around daylight which peaks around forenoon and during sundown before dusk[3]. Female aegypti mosquitoes nourish on blood several times between each blundering period[4]. The eggs after being laid remain viable for several months or if they come in contact with water they will hatch. As for Malaysia, the serotypes available circulating from 2000 to 2012 were the DENV1, DENV2, DENV3 and DENV4 serotypes. But each serotype predominantly varied over time and between states of Malaysia.

Although the case fatality rate is low among dengue patients, identification of mortality-related risk factors may help in patient management to reduce mortality by tackling the risk factors. According to a study, dengue patients with an age of > 50 years old have a two-fold greater risk of dying compared to patients with an age of 1-14 years old[5]. This might be due to the comorbidities which are more prevalent in this age group[5]. However, some studies show contradicting results regarding age. A study stated that the senescence group are discovered to be related with very bad dengue in France while another study stated that the rate of dengue mortality in Vietnam was highest among young children[6].

While In Brazil, studies discussed the role of gender in predicting mortality. Men show a higher mortality rate than women in dengue cases might be due to men tend to seek health services less frequently than women do which will then impede the opportunity for identification and treatment of dengue fever. This emphasises not only biological explanation but also behavioural risk factors[5]. These sexual variances could also be due to a gap in biological functions or psychological wellness towards looking out for the general well-being of one self[6].

Another factor for dengue mortality is bleeding. A case-control research was regulated in Kanchi Kamakoti Childs Trust Hospital located in Chennai that aimed to recognize the factors for unbidden bleeding phenomenon in Dengue sickness in youngsters populations cited a study that is conducted in the Philippines that stated the patients with platelets count less than 50,000/mm3 are having a six-fold spike in the possibility for mortality[7]. Another retrospective

study organised at Queen Sirikit National Institute of Child Health (QSNICH) which is situated in Bangkok, Thailand that aimed to find the frequency of Dengue shock syndrome (DSS) in an emergency room and to assess the medical intervention and aetiology corresponding with the after-effect of Dengue shock syndrome cases, stated that the case fatality rate was 8.8% and 35.6% of the dengue patients who died suffers from massive bleeding on presenting to the emergency department[8]. A retrospective cohort study stated that alarming plasma leakage was related to death in all patients in the 2013 Malaysian national dengue (e-Dengue) registry (OR 14.72; CI: 1.54 – 140.70)[6]. Another study done to recognize the aetiology related with mortality among patients with severe dengue, situated in the area of Amazonas region within the time frame from 2001 to 2013 showed that 4% of death cases resulted from plasma extravasation[9]. Based on a study conducted in Ho Chi Minh City, it is stated that dengue shock syndrome is a lethal intricacy of dengue and is proven by the results showing that generally, the case fatality rate (CFR) that includes the study population within the time frame of 1996 until 2009 was 0.25% (325 of 132,480)[10]. Because of these inconclusive findings, this study aims to systematically review studies to recognize the health risk that may lead the patients to mortality within dengue patients in Malaysia.

Material and methods

The systematic review paper was performed by utilising three databases, which is EBSCO, PubMed and lastly including ScienceDirect as our main articles searching and screening platform, in consideration of the easy access and wide coverage of dependable journals, approaching the factors and predictors of mortality among Dengue patients in Malaysia from January 2000 until December 2020. The search was limited to the last 20 years to collect as many significant findings related to the predictors of dengue mortality. The search strategy was adapted from the guideline of PRISMA which is the Preferred Reporting Items for Systematic Reviews. A preliminary search was done to pinpoint applicable keywords and determine whether this review was viable. The related keywords then were used to search for this review using online thesauruses, online dictionaries and online encyclopaedias. To achieve more accuracy in search results, both manual and advanced searching techniques were applied. On advanced search, the terms used in screening articles through databases includes, “Dengue” and “Mortality”, “Dengue” and “factors'', “Mortality” and “haemorrhagic fever”, “Dengue” and “Outcomes'', “Dengue” and “Malaysia''.

Selection criteria

The systematic review process started with a screening of the articles where titles, abstracts, study objectives, study design, place of study, and date of publication were screened based on inclusion and exclusion criteria for study selection. Articles within 20 years range from 1/1/2000 until 31/12/2020, Open access articles, English articles, study location in Malaysia, and observational studies such as cohort, cross-sectional and case-control studies were included in the inclusion criteria. For exclusion criteria, articles with no dengue infection, no mortality statistics, unsuitable abstracts, systematic review, peer-reviewed paper, program evaluation and qualitative studies, no control group such as non-fatal

group, and studies in severe dengue patients only were excluded in this systematic review. The remaining articles were then reviewed for the study results and any duplications of the articles were removed. The Mendeley reference manager will be used to manage the references for this systematic review.

Data Extraction Tool

The data extraction was adapted from the Cochrane Data Collection Form by all researchers and inserted into an Excel spreadsheet. Then, the data were categorised based on their (a) number; (b) titles; (c) date of publish; (d) study design; (e) country; (f) author; (g) aim of study; (h) factors. A second reviewer double-checked the articles assigned to them and gave comments in the table.

Quality Assessment of articles

The quality assessment tool used was adopted from Hoy et. al. to act as an indication of the strength of evidence the article provided. The quality of articles taken into account the appropriateness of the study designs from the article, risks of any bias in the article, intervention and reporting quality of the review. In case a discrepancy in scores happens, two reviewers are involved to discuss in detail and reach a consensus on appraising the articles. The third independent reviewer was referred if there is any disagreement between both reviewers. The articles were scored based on three domains and then summarised in which are the low chance of bias, moderate chance of bias and high chance of bias. The reviewers rated the quality score of the studies based on the text and will evaluate the quality based on the entries that are provided. A good quality article will have a lower risk of bias.

Result and Discussion

The initial search resulted in the selection of 523 studies, 83 studies were retrieved from PubMed, 332 studies from EBSCO and 108 studies from ScienceDirect. Out of 523 studies, a total of 60 duplicated articles were removed. The remaining 463 articles were then sieved and only the relevant articles were chosen to include in our studies. A total of 4 articles were selected for our research paper (Figure1).

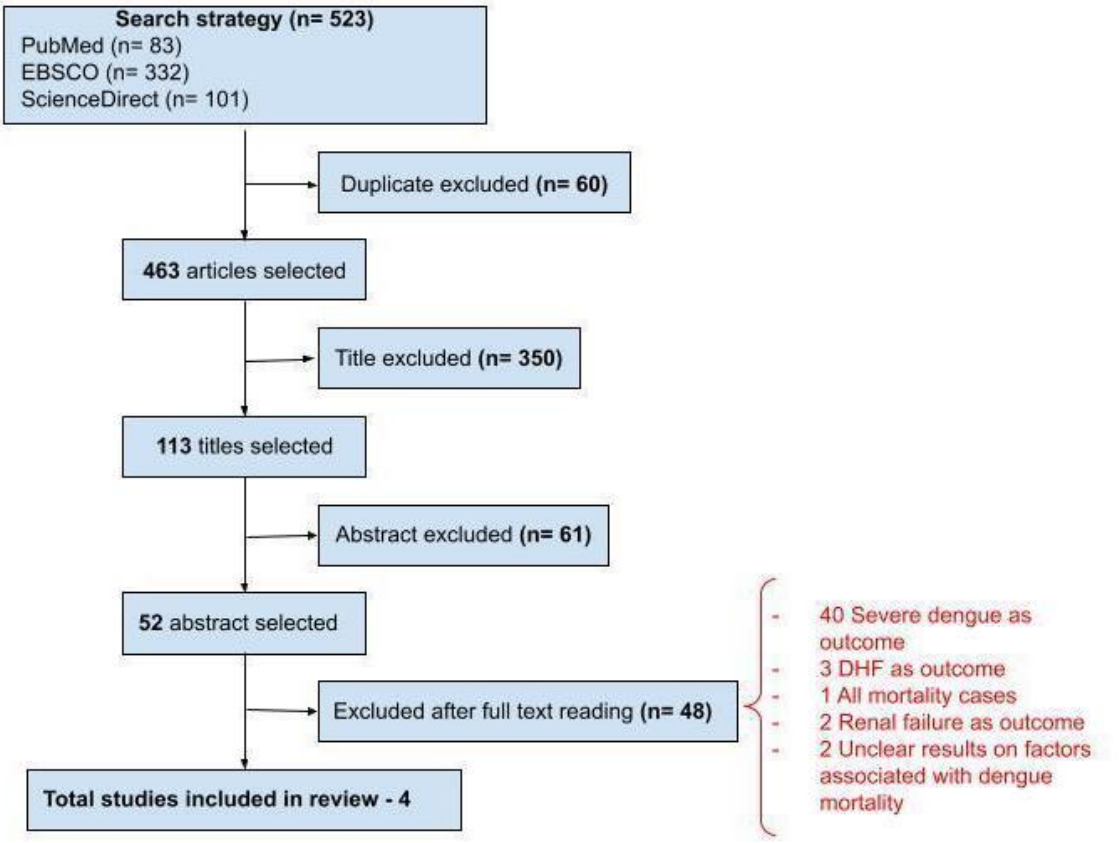

Figure 1: PRISMA flowchart

Table 1 contains a summary of all four articles that were screened and reviewed. The table consists of the title, study objective, method, factors, place of study, mean age, gender and prevalence that were related to dengue mortality. The table was made to organise our thoughts and rearrange the factors that we have found.

All of the factors extracted from the reviewed paper were further divided into six classifications namely age, gender, clinical manifestation, lab results, comorbidities and dengue complications. Figure 2 portrays the conceptual framework of our research. Based on our data, we can conclude that increasing age and bleeding contribute to mortality in two out of four articles.

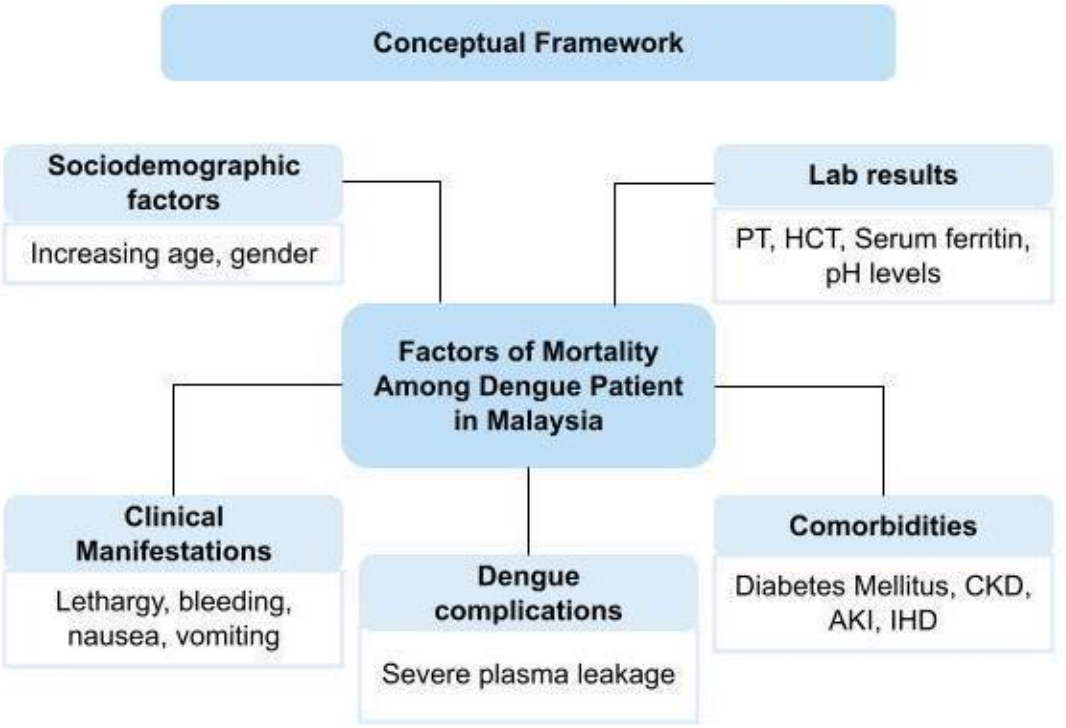

Figure 2: Conceptual Framework on Factors of Mortality Among Dengue Patients in Malaysia

Sociodemographic factors

Our data shows that two out of four studies mentioned that increasing age is one of the factors that leads to mortality in dengue patients.

Based on the Malaysian National Dengue Registry during the year 2013, among serologically confirmed patients, mortality was associated with increasing age and remained a significant associated factor among the adult population with a p-value of <0.001[6]. Similarly, in another cross-sectional retrospective study, it is stated that the overall mortality number in the age group of >40 years was 1.1% and thus, it is known to be one of the factors associated with dengue mortality (p-value=0.004)[11]. A higher risk of dengue related lethality with an escalation of age may be due to the declining biological performance and underlying comorbidities with older populations[12].

Besides that, gender was also an associated factor where two out of four articles discuss gender differences and their associations with dengue mortality. Out of the 2 articles, one article specifically mentioned that the female gender has a higher mortality rate compared to men and on the contrary, the other article mentioned that man is one of the factors of dengue mortality.

The female gender was found to be related with possible dengue fatality (OR 1.53; CI: 1.01-2.33)[6]. This observation might be due to females having a higher tendency to progress to having Dengue haemorrhagic fever (DHF)/ Dengue Shock Syndrome (DSS) with higher fatality numbers in comparison to males[13]. On the contrary, out of 15 mortality cases over 32 months seen in another retrospective study, 73% of them were males[14]. However, studies still have contradicting proof on the relation of gender with dengue mortality [6].

Clinical manifestation

Different articles mentioned different manifestations in different patients. Two out of four studies mentioned nausea, vomiting, bleeding and plasma leakage as the manifestations in mortality patients. Besides that, One article mentioned lethargy and/or restlessness, abdominal pain, retro-orbital pain, dysuria, shock, pleural effusion and ascites as the clinical features contributing to dengue mortality.

In the serologically confirmed group; persistent vomiting (OR 13.34; CI: 1.92–92.95) and bleeding (OR 5.84; CI 2.17–15.70) were associated with dengue related fatality, while in the general sample pool; nausea and/or vomiting, bleeding and lethargy and/or restlessness were associated with dengue related fatality with an OR value of 1.80, 3.01 and 5.97 respectively[6]. There is also another study that aligns with the finding of bleeding and leaking manifestation that contributed to mortality cases. For over 32 months, at a state hospital in Malaysia, a total of 15 samples that were associated with death were recorded, in which 80% had bleeding and leaking manifestation. A total number of 40% of cases had occult bleeding while 26.7% bled from the gastrointestinal system and oral cavity[14]. In another study, it is shown that nausea, vomiting, abdominal pain and fever were present in all death cases (100%) while pain behind the eyes and painful micturition presented in six out of eight patients (75%)[11]. Abdominal pain or tenderness was more frequently observed in adults[15]. Other than that, 60% of 15 mortality cases had pleural effusion while 61% developed ascites respectively, based on clinical, radiological signs and symptoms[14].

Vomiting and/or feeling nauseated should be considered as a prodromal indicator since it has presented in a significant number of patients. However, it is the only clinical manifestation that was not mentioned as one of the warning signs in the guideline recommendations. Patients with warning signs need to be monitored closely by the attending health care practitioner as these symptoms can lead to serious complications and dehydration due to reduced fluid intake[6].

Lab results

Upon doing further investigation on the dengue patient, lab results can reveal some factors contributing to dengue mortality. 3 out of 4 articles mention lab results as a contributing factor to dengue mortality. The said factors are (1) WBC count (2) Hematocrit level (3) Prothrombin time (4) Serum ferritin (5) pH level (6) Lactate levels and (7) Creatinine levels. Both hematocrit level and prothrombin time did contribute to the cause of the bleeding manifestation in patients infected with dengue.

According to a study with a percentage of 73% of the total fatalities, it is noted that the serum level of ferritin was >10,000 ng/mL in which 93.3% (n = 14) had serum pH lower than 7.35 and 100% had lactate higher than two. Prolonged PT and haematocrit levels of >20% with a p-value of 0.022 and 0.001 accordingly, were statistically significant that were linked with dengue mortality[11]. In a multivariate analysis, the significant indicators include WBC and creatinine with p-value of 0.002 and 0.015 accordingly. At a cut-off of 7 mmol/l of WBC and 131.5 mmol/l of creatinine, in Area Under Receiving Operative Characteristic (AUROC) was 0.896 ($p < 0.001$), showing that these were strong factors of dengue fatalities in severe dengue patients[18]

Comorbidities

Other than that, only 1 out of 4 articles mentions comorbidities as one of the factors leading to dengue mortality. Examples of comorbidities found that lead to death were;- Diabetes Mellitus (DM), Chronic Kidney Disease (CKD) and Ischemic Heart Disease (IHD)[11]. 50% of the fatality cases were due to underlying comorbid conditions.

In an overall 8 fatal cases based on a study conducted at Hospital Universiti Sains Malaysia (HUSM), 50% of patients were having at least two comorbidities (p =0.007). Results of this cross-sectional retrospective analysis demonstrated a significantly higher proportion of diabetes mellitus (DM) (p =0.007) and ischaemic heart disease (IHD) (p = 0.033) among reported fatality cases in comparison with patients who survived[11].

According to current and previous studies, in the presence of both dengue infection and underlying comorbidities as mentioned earlier, fatality rates were higher than in individuals with no underlying comorbidities. The reason for death in dengue cases with co-morbidities may be due to the progression of concomitant diseases itself, and not due to the dengue infection straightforwardly, especially in adults[13]. This data shows that patients who have comorbidities that are infected with dengue infection should be monitored closely and more particularly compared to patients who do not have comorbidities, as each patient should be managed differently according to their conditions. The pre-existing diseases that are not being managed accordingly can cost people's lives.

Dengue complications

Dengue affects the body as a whole in which the infection can lead to complications manifesting as diseases of another organ. One study mentioned that severe plasma leakage as a complication of dengue fever contributes to the majority of the dengue death rate. Dengue virus can attack respiratory systems which manifests as respiratory failure and pleural effusion that later leads to ascites as mentioned in one article. Besides respiratory systems, one article did mention that dengue fever can cause Acute Kidney Injury which deteriorates the patient's condition and eventually causes death. Moreover, our research revealed that dengue can cause multiple organ failures and develop secondary infections [11]. Since dengue is a systemic disease, one article stated that a number of their patients who had a shock as their complications died due to dengue fever.

Another article also mentioned that myocarditis secondary to dengue fever can be a contributing factor to dengue mortality.

In a study conducted, 60% of 15 mortality cases presented with manifestations of pleural effusion while 61% of the cases developed Ascites accordingly. In cases who suffered from renal failure requiring them to undergo continuous renal replacement therapy (CRRT) accounted for about 93.3% ($n = 14$) of mortalities, while 93.3% had severe hepatitis, 53% with myocarditis and 27% of mortalities cases had CNS (central nervous system) manifestations[14].

In the overall study population of cases in the Malaysian Dengue Registry taken from the year 2013, severe plasma leakage together with shock were also risk associated with probable dengue fatalities. Early detection of bleeding and plasma leakage is important by continuously keeping track of the haematocrit parameters during the critical phase; hence physicians can adjust the value of intravenous fluid administration to fend off severe plasma leakage, therefore, avoiding the development of shock[6]. Other than that, a study also mentioned the occurrence of acute kidney injury ($p < 0.001$), different organ failure ($p < 0.001$), rhabdomyolysis ($p < 0.001$) and respiratory failure ($p = 0.007$) also contributed to factors related to dengue fatalities in a general fatality rate of 1.1% of 667 patients[11]. Moreover, the entirety of lethal cases had suffered from a late stage of acute kidney injury (AKI) together with several organ injuries.

Finally, a secondary infection that usually correlates to disease severity was mentioned in a study conducted in Hospital Universiti Sains Malaysia (HUSM) whereby out of 8 fatal cases, three had secondary infection[11]. Current data in our systematic review showed many complications that can lead to mortality among dengue patients in Malaysia. Whether it is a common or uncommon complication, the medical team needs to be attentive and aware at all times of the development of any complications in dengue patients so they can be treated appropriately and effectively. Hence, with the identified potential factors for dengue mortality, it is encouraged that more predictive models can be developed based on this factor and an extensive study for meta-analysis of the factors that have been identified.

As for the strength of the study, this systematic review covers a comprehensive number of available articles in our research context due to the search and screening of articles process involving multiple reliable search engines that were widely used globally and the articles were included based on the study criteria that we have determined and listed. This study also had a reliable quality assessment and low possibility for bias due to the thorough exploration of risk for bias for each article had been conducted and the summary of the assessment had been included in order to minimise bias and inaccurate reporting of the selected articles. The study also adapted a dependable and trusted methodology strategy as the core and vital steps were adapted and referred from PRISMA guidelines that were utilised worldwide as the preferred method to report a systematic review. There were also lists of accepted and reviewed studies that are summarised in the table for easy referencing.

For this study limitations, our study has several limitations faced during conducting the study. Limitations for study identifications and literature search

were that a limited amount of search databases were accessible to our team due to financial hindrance, hence potential available articles might not be reviewed. There were also not many available research articles emphasising on the mortality factors for dengue specifically in Malaysia so our team ended up with a few articles to be studied according to our screening protocol hence leading to a less strong factor evidenced by the previous studied articles.

Quality assessment table:

Entry	Liew et al., 2016	Mallhi et al., 2017	Omar et al., 2020	Thabit et al., 2020
Do the research selected populations is a near portrayal of the nations communities in associations to the applicable variables?	Low probability Comment: Probably done. The paper reports study subjects were taken through the national registry of dengue and contains various sociodemographic factors.	Low probability Comment: Probably done. In the paper. It is stated that the target population is in the area of highly reported dengue cases in Malaysia.	Low probability Comment: Probably done. The author stated that the samples were taken from the dengue fatality cases from University Malaya Medical Centre (UMMC).	Low probability Comment: Probably done. Data entries were taken from medical records from confirmed dengue mortality.
Does the sampling frame show a true or firm depiction of the target population?	Low probability Comment: Probably done as the data were taken from the national data registry focussing on dengue mortality representing the true or close target population.	Low probability Comment: Probably done. Data obtained via form that has been reviewed by the hospital ethical committee.	Low probability Comment: Probably done. The samples were taken by considering various factors and are in close relation with the target population.	Low probability Comment: Probably done. Data were taken considering only dengue mortalities.
Do the data obtained utilise a random selection technique?	High probability Comment: Probably not done.	Low probability Comment: Probably done. The author did state that samples were	High probability Comment: Probably not done. The author stated that all the samples that fulfil	High probability Comment: Probably not done. The data was taken as long as it

		taken randomly and covered all layers of Malaysia's populations.	dengue infections fatalities were included in the study.	represents dengue mortality.
Do the nonresponse bias have a minimal chance?	Low probability Comment: Probably done. This is evidenced by the data taken from the national registry and has low risk for dropout.	Low probability Comment: Probably done. Author emphasised the samples were obtained directly and given codes to identify them accurately.	Low probability Comment: Probably done. The data was taken from the cases that fulfil the dengue mortality from University Malaya Medical Centre (UMMC).	Low probability Comment: Probably done and the risk of nonresponse bias is low.
Do the data obtained straight from the subjects instead of using representatives or any involvement of a third party organisation?	High probability Comment: Probably not done.	Low probability Comment: Probably done. Samples were taken directly with only confirmed dengue infected patients only with proper identification for each patient.	High probability Comment:Probably not done. The author takes the fatality cases from University Malaya Medical Centre (UMMC).	High probability Comment: Probably not done. The data was taken through medical records of deceased dengue patients.
Do the study paper utilise a justifiable case definition?	Low probability Comment: Probably done, the author emphasised the clinical criteria used to diagnose dengue.	Low probability Comment: Probably done. The author did state clinical parameters to confirm dengue cases while the research was	Low probability Comment:Probably done. The author just states that there are important presentations of dengue on the samples before deciding to accept	Low probability Comment: Probably done. The author mentioned the dengue cases were obtained via laboratory confirmed dengue cases.

		ongoing	the data.	
Do the articles mentioned the study apparatus utilised that computes the framework of interest having reliability and validity?	Low probability Comment: Probably done. The author stated the instrument they used and the outcomes that they sought.	Low probability. Comment: Probably done. Author did mention the apparatus used to carry out data evaluations.	Low probability Comment: Probably done. The author mention the type of statistical analysis used and relevant statistical model to provide the outcomes	High probability Comment: Probably not done.
Did all the articles utilise the similar mode data collection?	Low probability Comment: Probably done. The paper did use the similar mode of data collection throughout the research period.	Low probability Comment: Probably done. The author mentioned the data collection method was uniform for all samples in the study.	Low probability Comment: Probably done. The cases obtained in this study utilised identical data collection mode for all the samples included.	Low probability Comment: Probably done. The author stated that the data obtained were through medical records of the Hospital Tengku Ampuan Rahimah, Klang throughout the study.
Conclusion towards the risk of bias evaluated.	Low chance of bias	Low chance of bias	Low chance of bias	Moderate chance of bias

Table 1: Main finding

No	Title	Author/Year	Objective	Method	Factors	Place of Study	Mean age	Gender	Prevalence
1	Dengue in Malaysia: Factors associated with dengue mortality from a National Registry	Liew et al., 2016	To determine the factors associated with dengue-related mortality	Retrospective cohort study	1. Increasing age (OR 1.03; CI:1.01–1.05) 2. Persistent vomiting (OR 13.34; CI: 1.92–92.95) 3. Bleeding (OR 5.84; CI 2.17–15.70) 4. Severe plasma leakage (OR 66.68; CI: 9.13–487.23)	Malaysia	41.8 years (SD 20.5)	45.7% Male 54.3% Female	92 deaths out of 43 347 cases patients with dengue
2	Determinants of mortality and prolonged hospital stay among dengue patients attending tertiary care hospital: a cross-sectional retrospective analysis.	Mallhi et al., 2017	To determine the significant factors associated with dengue-related prolonged hospitalisation and death.	Cross-sectional retrospective study	1. Age >40 years (p=0.004) 2. Secondary infection ($p = 0.040$) 3. Comorbidities ($p<0.05$) 4. Acute kidney injury ($p<0.001$) 5. Prolonged PT ($p = 0.022$) 6. Multiple-organ dysfunctions (p	Kelantan	48.8 ± 25.6 years		Overall case fatality rate was 1.1%

					<0.001) 7. Haematocrit >20% (p = 0.001) 8. Rhabdomyolysis (p <0.001) 9. Respiratory failure (p = 0.007)				
3	Predictors of dengue mortality among severe dengue patients in University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia	Omar et al., 2020	To determine the significant variables that can be used to predict dengue mortality	Retrospective	1. WBC with Adjusted Odds Ratio (AOR) = 0.644, p = 0.002 (95% CI: 0.489–0.849) 2. Creatinine with AOR = 0.992, p = 0.015 (95% CI: 0.986–0.999)	University Malaya Medical Centre (UMMC)	43.69 years (SD 15.9)		18 deaths out of 5246 cases from January 2015 to March 2019

4	Retrospective analysis of dengue mortalities over a 32. month period in a state hospital, Malaysia	Thabit et al., 2020	To study the complications and predominant clinical manifestations associated with dengue mortality and correlate the mortalities with the dengue serotypes over 32 months.	Retrospective study	1. 73% males 2. 80% bleeding manifestations 3. 60% pleural effusion 4. 61% ascites 5. 93.3% serum pH <7.35 6. 100% lactate >2 7. 73% Serum ferritin >10,000 ng/mL 8. 93.3% renal failure 9. 93.3% severe hepatitis 10. 53% myocarditis 11. 27% CNS manifestations	Klang, Selangor		73% Males 27% Females	A total of 15 mortality cases over 32 months

Conclusions

In this study, several predictive factors for dengue mortality have been recognized. To conclude we recognized that age and bleeding are the factors that have a higher risk of mortality that may contribute to exacerbating the patient conditions and thus causing mortality. Hence, clinicians should be vigilant of these factors and monitor them closely and provide necessary measures to prevent the condition from getting execrable. Despite the mortality rate in Malaysia decreasing, effective interventions and enforcement should be done by authorities together with society to combat the dengue outbreak while lessening the complications as well as mortality rate.

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