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Meteorological predictors of dengue hemorrhagic fever incidence in Cilacap Regency, Indonesia: A time series analysis

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ABSTRACT

Objective: To analyze the nonlinear relationship between meteorological predictors and dengue hemorrhagic fever, and to quantify the meteorologically attributable fraction of dengue hemorrhagic fever (DHF) during 2021–2025 in Cilacap Regency.

Methods: This ecological time series design used sequential three-stage analytical tools, including a cross-correlation function (CCF) analysis applied to identify lag structures, Granger causality within a vector autoregression (VAR) framework used to confirm directional temporal precedence, and a quasi-Poisson Distributed Lag Nonlinear Model (DLNM) with natural cubic spline crossbases over a 28-day lag window used to estimate the exposure-response relationship. Autoregressive terms alongside long-term trends and seasonal splines were incorporated to account for autocorrelation and potential confounding.

Results: Granger causality testing confirmed unidirectional of DHF relationships across all four predictors, including mean temperature, rainfall, relative humidity, and wind speed (all $P < 0.05$). Among these, daily rainfall emerged as the dominant predictor [relative risk (RR) 4.23; 95% CI 2.10–8.52], a peak CCF lag of 7 days, and an attributable fraction of 27.58%. The mean temperature displayed a J-shaped exposure-response curve, with a protective nadir at 26.5 °C, and markedly elevated risk above 28 °C [RR 2.13; 95% CI 1.43–3.19; Attributable Fraction (AF) = 6.22%]. Relative humidity (AF = -14.40%) and wind speed (AF = -3.37%) demonstrated complex nonlinear patterns contributing net protective attributable fractions. Overall, the model explained 52.26% of the null deviance (QAIC = 3984.23).

Summary

Question: How do meteorological predictor relate to dengue hemorrhagic fever (DHF) incidence, including their lagged, nonlinear, temporal effects, and attributable fraction?

Findings: 2846 DHF cases were recorded in Cilacap Regency during 2021–2025. This study confirmed the unidirectional temporal precedence of meteorological predictor over DHF incidence. Rainfall and temperature were the most strongly associated meteorological predictors, operating through lag windows of 7 and 11 days, respectively. Additionally, rainfall was the dominant meteorological predictor to the DHF incidence with attributable fraction (AF) of 27.58%, followed by temperature with 6.22%.

Meaning: Vector control program and early warning system of DHF in Cilacap should consider the utilization of meteorological predictor to prevent the DHF outbreak.

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Conclusions: Rainfall and temperature were the meteorological predictors most strongly associated with DHF incidence in Cilacap Regency. This finding provides evidence for actionable vector control program and early warning system of DHF to consider the utilization of meteorological predictor to prevent DHF outbreak in Cilacap.

KEYWORDS: Tropical disease; Vector-borne disease; Distributed Lag Nonlinear Model; Rainfall; Temperature; Early warning system

1. Introduction

Among mosquito-borne viral diseases, dengue has the adverse global public health consequences, and its geographic reach continues to expand at an alarming pace. The World Health Organization indicates that approximately 100-400 million dengue infections occur annually, by which 96 million are clinically apparent, placing nearly 3.9 billion people at risk across more than 120 countries, predominantly in tropical and subtropical regions[1]. These estimates are broadly consistent with earlier modelling studies, which suggested up to 390 million infections per year[2]. Over the past two decades, the incidence of dengue has increased substantially, driven by a combination of rapid urbanization, population mobility, and environmental changes, including climate variability and long-term climate change. More recent epidemiological assessments indicate that climate-sensitive vector-borne diseases such as dengue are expected to intensify further under future warming scenarios, particularly in Southeast Asia[3].

In Southeast Asia, dengue transmission remains a major public health concern, and Indonesia consistently reports one of the highest burdens in the region. National surveillance data indicate a substantial increase in dengue cases in 2024, reaching approximately 149 866 reported cases by mid-year. Dengue hemorrhagic fever (DHF), a severe manifestation of dengue infection, has long been the principal concern of surveillance systems and control programs. Improved clinical management has reduced case fatality rates. However, this progress has not translated into a reduction in case number. In contrast, the absolute incidence continues increase[4]. The persistence of this trend underscores the role of environmental factors that contributes DHF transmission dynamics.

Dengue transmission is not meteorologically independent. Weather conditions actively shape the biological capacity of *Aedes* mosquitoes to acquire, incubate, and transmit the dengue virus. Temperature play vital role to this relationship, by accelerating larvae mature process, increasing survival rate and feeding activity of adult mosquitoes, including shortening the extrinsic incubation period within the vector[5]. Rainfall creates and replenishes the standing water

bodies on which the larvae depend, and increasing vector density. However, heavy rainfall can wash the larvae away, which explains the nonlinear patterns[6]. Humidity protects adult mosquitoes from desiccation, including extend their active lifespan. On the other hand, wind conditions may whether facilitate or constrain dispersal and the ability to locate a host[7]. Taken together, these meteorological exposures are rarely straightforward in DHF transmission, where threshold values, saturation points, and optimal ranges define these relationships far better than any linear model does.

The climate-dengue relationship is well-established in principle. However, the literature is riddled with methodological inconsistencies that limit the depth and reliability of conclusions. Chief among these is the widespread use of weekly or monthly aggregated data that makes it difficult to recover the short-term lag structures[8,9]. Another problem is the assumption of linearity in exposure-response modelling, which sits uneasily alongside entomological evidence regarding threshold effects and optimal meteorological ranges for vector activity. The Distributed Lag Nonlinear Model (DLNM) framework was developed partly in response to these concerns, offering a flexible tool for simultaneously estimating delayed and non-linear environmental effects on disease outcome[8]. Nevertheless, DLNM studies routinely fall short in two respects, including lag windows tend to be chosen arbitrarily rather than derived from empirical data, and the causal direction of observed associations is seldom formally evaluated. Both gaps have operational consequences where lag structures are unvalidated and causal directionality is assumed rather than demonstrated, early warning models built on these foundations are inherently fragile. Pairing the DLNM with cross-correlation function (CCF) analysis for lag identification and Granger causality testing within a vector autoregression (VAR) framework addresses these shortcomings directly, grounding temporal inference in a more defensible evidential sequence[10] for a disease such as DHF. This methodological rigor is not merely desirable but operationally necessary.

Despite its sustained DHF burden and ecological significance as a coastal-agricultural interface zone, no daily resolution DLNM analysis of the meteorological determinants of DHF has been conducted in Cilacap Regency. Cilacap Regency, located on the southern coast of Central Java, Indonesia, represents an ecologically significant and epidemiologically understudied setting for dengue transmission. As a humid tropical climate area strongly influenced by the Southern Oscillation monsoon system, Cilacap experiences marked inter-annual meteorological variability consistent with conditions conducive to *Aedes (Ae.) aegypti* population dynamics. Nevertheless, Cilacap is reporting a sustained DHF burden and exhibiting marked inter-annual variability in incidence, including a pronounced trough in 2023, it follows high-burden years in

2021 and 2022. This gap is critical in the context of the increasing demand for locally calibrated, short-term predictive models to support district-level dengue early warning systems in Indonesia. Therefore, this study aimed to: a) identify the empirical lag structure of meteorological-DHF associations using CCF analysis, b) assess temporal directionality using Granger causality within a VAR framework, c) quantify the nonlinear and lagged effects of temperature, rainfall, relative humidity, and wind speed on daily DHF incidence using a DLNM, and d) estimate the attributable fraction of DHF burden associated with each meteorological factor.

2. Methods

2.1. Study design

This study employed an ecological time series design to investigate lagged, nonlinear associations between daily meteorological predictors and DHF by using daily aggregate data at the district level. Time series analysis can be defined as the examination of data collected over time, where observations are recorded or aggregated regularly, which is widely used in ecology[11]. An ecological time series study can be used for forecasting, regression modeling, or trend and seasonality extraction[12]. This design was appropriate for evaluating the temporal relationship between meteorological predictors as environmental exposure and DHF cases.

2.2. Study setting and period

This study was conducted in Cilacap Regency. Statistics Indonesia, also known as Badan Pusat Statistik, reported that Cilacap, a southern area of Central Java Province in Indonesia, has the largest geographical area (2249.28 km², or 6.77%)[13]. Cilacap has 24 subdistricts with 284 villages and urban wards. In 2025, the total population was 2046392, with a population density of 881 people/km². Cilacap was selected as the study area because of its endemicity to dengue, with a consistently fluctuating case incidence over time. Cilacap has a tropical climate with wet and dry seasons. Cilacap also has diverse geographical and climatic characteristics, including coastal, lagoon, and inland regions. Furthermore, complete and continuous daily data on DHF cases are available. This study period was set from 2021 to 2025 to capture temporal variations in dengue incidence and meteorological predictors (1818 observation days; analytic sample after autoregressive lag adjustment $n=1811$ days), including seasonal patterns. This timeframe enabled the identification of fluctuations, lag effects, and a more robust temporal relationship between meteorological predictors and DHF incidence. The data themselves were analysed in April 2026.

2.3. Data and variables

The outcome variable in this study is the daily number of DHF cases in Cilacap from 2021 to 2025. The diagnosis of DHF was made by physicians based on a combination of clinical and laboratory assessments. Clinically, it is characterized by symptoms such as fever, hemorrhagic manifestations, headache, weakness, nausea or vomiting, muscle and joint pain, retro-orbital pain, rash, hypotension, hepatomegaly, and restlessness. Laboratory examination included hematological parameters such as platelet count (per mm³), hemoglobin level (g/dL), and hematocrit (%), as well as dengue-specific diagnostic tests, including NS1 antigen and rapid diagnostic tests for IgG and IgM. These assessments collectively support the diagnosis and allow the evaluation of disease severity.

The predictor variables in this study are mean temperature (°C), rainfall (mm), relative humidity (%), wind speed (m/s), and flood events. Local climate data were obtained from the Indonesian Agency for Meteorology, Climatology, and Geophysics (BMKG), which provides accessible, consistent, and long-term meteorological data through its online platform (<https://dataonline.bmkg.go.id/dataonline-home>). Such data are essential for identifying trends and temporal changes in local climate conditions[14].

In this study, rainfall is operationally defined as the average amount of precipitation measured in millimeters within a specific area over a defined period. Temperature refers to the average level of atmospheric heat, expressed in degrees celsius (°C), and represents the intensity of molecular activity in the air over a given time frame. Relative humidity is defined as the concentration of water vapor in the air at a particular time and is expressed as a percentage (%). Wind speed is defined as the rate of air movement in the atmosphere, measured in meters per second (m/s), over a specified period.

Flood occurrences were obtained from the National Agency for Disaster Countermeasure database (<https://dibi.bnppb.go.id/superset/dashboard/2/>). A flood event was operationally defined as any documented occurrence of water inundation in which the volume of flow exceeded the normal capacity of existing drainage infrastructure or river channels, resulting in the submergence of land areas not ordinarily subject to standing water, as captured through a daily binary indicator variable.

2.4. Data processing

The primary dataset, comprising daily DHF case counts and local meteorological predictors, was obtained in *xls format. Preliminary screening of the DHF records revealed no missing values. However, the meteorological dataset required structured preprocessing prior to analysis, which was performed using Python within a Jupyter Notebook environment, leveraging the pandas and NumPy libraries. An initial inspection revealed missing values encoded as nonstandard

placeholders, specifically the string "-" and the numeric code "8888," which introduced mixed data types across several variables. Data type harmonization was therefore performed as a first step, with all irregular entries recoded as missing (NaN) before conversion to the appropriate numeric formats. A descriptive assessment of the missingness patterns revealed variable proportions of missing data across the meteorological fields. Specifically, missing values accounted for 0.88% of the temperature observations, 0.77% of the relative humidity, 19.09% of the rainfall, and 0% of the wind speed records. Given that the missing segments were short and temporally discontinuous, linear interpolation was preferred over multiple imputation or Kalman smoothing, which is consistent with the established practice for short gaps in environmental time series[15–17]. Following imputation, the dataset was verified to be complete with no residual missing values.

2.5. Variable transformation

Before model specification, the distributional characteristics of all the predictor variables were examined using skewness statistics. Daily rainfall displayed severe positive skewness (skewness=6.26), a pattern driven by the high frequency of dry days with zero precipitation and sporadic extreme rainfall events reaching 356.0 mm. To address this, rainfall values were log-transformed as $\log(\text{rainfall} + 0.1)$ prior to crossbasis construction, with a constant of 0.1 incorporated to handle zero-valued observations. The resulting transformed series achieved a near-symmetrical distribution, with the skewness reduced to approximately zero (0.001), confirming satisfactory normalization. The mean temperature (skewness=0.50), relative humidity (skewness=0.18), and wind speed (skewness=0.50) were within acceptable bounds and did not require any transformation. Daily DHF case counts were modeled directly as the outcome under a quasi-Poisson distributional assumption, which intrinsically accommodates right-skewed count data through the log-link function without requiring manual transformation of the outcome variable.

2.6. Statistical analysis

A sequential three-stage analytical framework was employed to ensure methodological rigor in the characterization of meteorological and DHF associations. In the first stage, a CCF analysis was used to identify the temporal lag structure of each meteorological predictor and provide empirical justification for the maximum lag window applied in subsequent analyses. In the second stage, Granger causality testing within a VAR framework was used to establish the directionality of associations prior to quantitative effect estimation. In the third stage, DLNM was fitted to simultaneously quantify the nonlinear exposure-response relationship and the full

lag dynamics of each meteorological predictor on DHF incidence. The staged analytical sequence, moving from descriptive correlation through formal direction testing to quantitative effect estimation, progressively builds an epidemiological case for a meteorological contribution to DHF transmission in Cilacap.

Three temporally distinct lag concept are used across this framework and are not interchangeable, namely: a) the empirical lag structure identified through the CCF analysis (stage 1, used descriptively to justify the model's lag windows), b) the 28-day maximum lag specified in the DLNM crossbasis functions (stage 3, governing the exposure-lag-response surface for each meteorological predictors), and c) short autoregressive lags (1 and 7 days) of the outcome series itself, included solely to address residual serial correlation in DHF case. These are defined separately in the subsections below:

2.6.1. Stationarity assessment

The stationarity of all the time series was evaluated using the Augmented Dickey-Fuller (ADF) test and the Kwiatkowski-Phillips-Schmidt-Shin (KPSS) test prior to the CCF analysis and VAR model fitting. All the variables returned statistically significant ADF statistics ($P \leq 0.01$). Conversely, all series yielded significant KPSS statistics ($P < 0.05$). This pattern of conflicting results between the ADF and KPSS tests is characteristic of time series exhibiting deterministic seasonal nonstationarity, where a series is stationary in mean but contains periodic fluctuations in level or variance driven by seasonal cycles[18]. Accordingly, all the variables were prewhitened by extracting Pearson residuals from regression models that controlled for long-term trends [ns (time, $df=8$)] and seasonal cycles [ns (doy, $df=4$)] prior to CCF computation. The "ns" term refers to a natural spline. For VAR-based Granger testing, the same detrended residual series was used as model inputs, satisfying the stationarity assumption of VAR estimation without recourse to differencing, which would have removed biologically meaningful lag structures.

2.6.2. Cross-correlation function (CCF) analysis

Cross-correlation functions were computed between the detrended residuals of each meteorological predictor and the detrended DHF case counts over lags of 0 to 28 days using the `ccf()` function in R. Detrending of the meteorological predictors was performed by extracting residuals from null regression model that included natural cubic splines of calendar time and day-of-year as sole predictors. DHF case counts were similarly detrended by extracting Pearson residual from a null quasi-Poisson model that additionally included day-of-week as a categorical covariate. This removed confounding from long-term trends and seasonal periodicity before assessing lagged correlation.

Individual lag correlations were evaluated for statistical significance against the asymptotic 95% confidence boundary of $\pm 1.96/\sqrt{n}$

$= \pm 0.046$, which was derived from a total observation length of 1811 days. The CCF results revealed significant cross-correlations extending up to 27 days across meteorological predictors, and this empirically derived lag structure served as the primary data-driven rationale for specifying a 28-day maximum lag window in the subsequent DLNM analysis.

2.6.3. Granger causality analysis

To evaluate the directional predictive relationship between meteorological predictors and DHF incidence, Granger causality testing was conducted within a VAR framework using the vars package in R[19]. The VAR model was fitted on a five-variable system comprising detrended residuals of DHF case counts, mean temperature, log-transformed rainfall, relative humidity, and wind speed. The optimal lag order was determined using information criteria: both Akaike information criterion (AIC) and final prediction error (FPE) selected $P=7$ lags, while Hannan-Quinn criterion (HQ) and Schwarz criterion (SC) selected $P=2$ and $P=1$, respectively. The AIC-selected lag of $P=7$ was adopted as the final specification on the grounds of information loss minimization, consistent with the 7-day peak CCF observed for rainfall and the weekly transmission periodicity of dengue. While the HQ and SC criteria favored more parsimonious specifications ($P=2$ and $P=1$, respectively), these shorter lag orders risk truncating the biological transmission window relevant to dengue. The $P=7$ specification is independently consistent with the weekly periodicity of dengue transmission documented in the literature[20], although this consistency was not used as the primary selection criterion.

Granger causality was tested for each meteorological predictor in the direction of meteorological exposure $\rightarrow$ DHF incidence, as well as in the reverse direction as an omnibus check for feedback effects. Unidirectional Granger causality from meteorological predictors to DHF incidence, without significant reverse causality, would support the validity of specifying meteorological predictors as antecedent exposures in the DLNM.

2.6.4. Distributed Lag Nonlinear Model

Crossbasis specification: DLNMs were fitted using the dlnm package (version 2024.12.0) in R[21,22]. The DLNM framework simultaneously estimates the shape of the exposure-response relationship and the temporal dynamics of lagged effects through a bidimensional crossbasis function, constructed as the tensor product of two marginal basis functions: one characterizing the exposure dimension and the other the lag dimension.

In the exposure dimension, a natural cubic spline with three degrees of freedom was specified for each meteorological predictor, with two internal knots placed at the 33rd and 67th percentiles of the observed distribution. The knot placements were as follows: 27.10 °C and 27.90 °C for mean temperature; 82.00% and 85.00% for relative humidity;

1.00 m/s and 2.00 m/s for wind speed; and -0.69 and 1.86 on the log scale (approximately 0.40 mm and 6.34 mm on the original scale, respectively) for log-transformed rainfall. Knot placement at these percentile positions was intended to capture potential threshold and plateau effects in the meteorological-DHF exposure-response relationship, which is consistent with the nonlinear biological dynamics of *Ae. aegypti* documented in the entomological literature[23].

In the lag dimension, a natural cubic spline with three degrees of freedom was applied over a maximum lag of 28 days, empirically supported by the results of the CCF analysis, which revealed significant cross-correlations extending to lag 27 days across multiple predictors, with a single internal knot placed at a lag of 14 days. This knot placement reflects the midpoint of the *Ae. aegypti* aquatic development phase and follows the established log-scale spacing conventions for lag splines[21,24].

2.6.5. Outcome model

Crossbasis functions for all four meteorological predictors (mean temperature (T_{avg}), log-transformed rainfall [log-relative risk (RR)], relative humidity (RH), and wind speed (ff)) were simultaneously included as predictors in a quasi-Poisson generalized linear model with a log-link function. The quasi-Poisson family was selected because of mild overdispersion in the daily case count outcome (quasi-dispersion=1.27). Long-term trends were controlled using a natural cubic spline of calendar time with eight degrees of freedom [$ns(time, df=8)$]. A seasonal cycle spline [$ns(doy, df=4)$] and day-of-week indicator [$factor(dow)$] were included to account for within-year seasonal patterns and reporting artifacts, respectively. Flood occurrence was included as a binary covariate. In addition to 28-day exposure-lag window specified in the meteorological crossbasis functions, short autoregressive terms at lags of 1 and 7 days (Y_{t-1} , Y_{t-7}) were separately incorporated to resolve residual autocorrelation, reducing the Pearson residual ACF at lag 1 from 0.21 to 0.02. The model was as follows:

$$\log E(Y_t) = \alpha + CB(T_{avg,t}) + CB(\log-RR_t) + CB(RH_t) + CB(ff_t) + \beta_1 Flood_t + \beta_2 Y_{t-1} + \beta_3 Y_{t-7} + ns(time, 8) + ns(doy, 4) + factor(DOW_t)$$

where $CB(\cdot)$ denotes the cross-basis matrix for each meteorological predictor and Y denotes the observed daily DHF cases.

2.6.6. Effect estimation and attributable fraction

Exposure-lag-response associations were quantified using the crosspred() function, which generated predictions across 100 evenly spaced exposure values spanning the observed range at each lag from 0 to 28 days. Relative risk estimates were computed with reference to the observed median value of each meteorological predictor: 27.60 °C for mean temperature, 2.00 mm (log scale: 0.74) for daily

rainfall, 83.00% for relative humidity, and 2.00 m/s for wind speed. Cumulative exposure-response curves integrating the lagged effect over lags 0–28 were derived using the `cumul = TRUE` argument.

Lag-specific relative risks were also extracted from the fitted DLNM to complement the cumulative estimates, by using the peak lag independently identified in the Stage 1 (CCF analysis) for each predictor. In addition, population attributable fractions (AFs) and attributable numbers (ANs) were estimated by interpolating the cumulative relative risk surface from the crosspred object to the observed daily exposure values. For each day t , the daily AF was computed as $AF_t = 1 - (1/RR_t)$, where RR_t is the cumulative relative risk corresponding to the observed exposure value on that day. The total AN were summed across the study period and expressed as a proportion of the total observed cases. Attributable fraction estimates are reported as point estimates only. Confidence intervals were not computed because bootstrap-based simulation (*e.g.*, *via* `attrdl`) was not implemented in the present analysis. Accordingly, the precision of the AF and AN value should be interpreted with appropriate caution.

2.6.7. Residual diagnostics

Residual autocorrelation was assessed iteratively throughout model development using the Ljung–Box test (lag 14) and inspection of the Pearson residual ACF. The initial DLNM exhibited pronounced residual autocorrelation (ACF lag-1 = 0.21; Ljung–Box statistic = 448.27, $P < 0.001$). The sequential addition of the seasonal spline [`ns(doy, df=4)`] and autoregressive terms (Y_{t-1} , Y_{t-7}) reduced the lag-1 ACF to 0.020, with a corresponding reduction in the Ljung–Box statistic to 80.26. Although formal statistical significance was retained owing to the large sample size ($n = 1\,811$), residual autocorrelation at lags 2–7 was uniformly less than 0.09, representing a magnitude attributable to inherent clustering of infectious disease transmission rather than model misspecification [25]. Because standard error for the crossbasis coefficients were derived from the standard quasi-poisson variance structure, this residual dependence may result in confidence intervals that marginally narrower.

2.6.8. Model fit and sensitivity analysis

Model fit was evaluated using the quasi-Akaike information criterion (QAIC), computed as $QAIC = -2 \log L/\phi^{\wedge} + 2k$, where $\log L$ is the Poisson log-likelihood evaluated at the fitted values, $\phi^{\wedge}$ is the estimated quasi-dispersion parameter, and k is the number of model parameters. The proportion of null deviance explained was additionally reported as a measure of overall model performance. The adequacy of the quasi-dispersion adjustment was verified using the Pearson χ^2/df ratio. To assess model robustness, sensitivity analyses were performed by varying the degrees of freedom allocated to the long-term trend spline across three values ($df=6, 8,$

and 10), while holding all remaining model parameters fixed. The specification associated with the lowest QAIC value was retained as the final model. A complete summary of all the candidate specifications and their corresponding fit statistics is presented in the Results section.

2.7. Ethical clearance

The ethical clearance of this study was approved by The Research Ethics Committee of Faculty of Health Sciences, Jenderal Soedirman University (No. 2255/EC/KEPK/IV/2026) on 6 April 2026.

3. Results

Over the five-year observation from January 2021 to December 2025, a total of 2846 DHF cases were recorded in Cilacap Regency. Notably, on 772 days (42.5%) of the total observation period, zero cases were recorded, reflecting the episodic and spatially clustered nature of DHF transmission in the region.

The monthly DHF burden was shown by Figure 1. Figure 1 highlights that the highest incidence was recorded in 2022 (898 cases), followed by 2024 (815 cases) and 2021 (656 cases). The lowest annual DHF case was recorded in 2023 with 103 cases. In 2025, 374 cases were recorded. The monthly distribution revealed a bimodal seasonal pattern, with peak transmission occurring during the first half of the year (January–May) and a pronounced trough in the dry season (August–September), which is consistent with the monsoon climate cycle of coastal Central Java Province, Indonesia.

The median (IQR) of temperature, relative humidity, daily rainfall, and wind speed during 2021–2025 are 27.60 °C (26.80–28.10 °C), 83% (81%–86%), 2 mm (0–10.6 mm), 2 m/s (1–2 m/s), respectively. Meanwhile, flood events were documented on 54 days (3%) in Cilacap Regency.

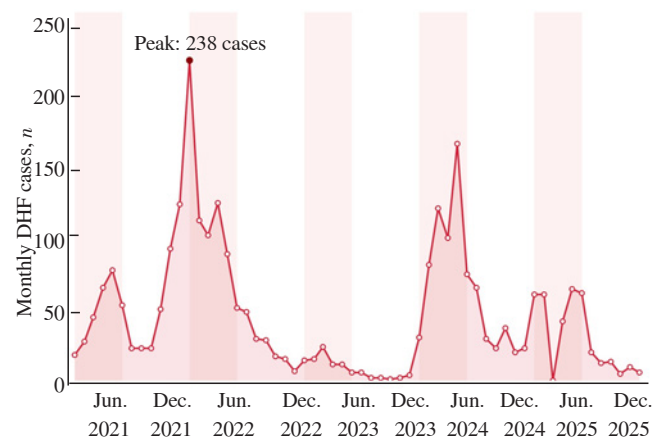


Figure 1. The trend of monthly dengue hemorrhagic fever cases in Cilacap Regency.

3.1. Stationarity assessment

All the time series exhibited a pattern of conflicting ADF and KPSS test results. This pattern is consistent with deterministic seasonal nonstationarity driven by the tropical monsoon cycle rather than stochastic unit-root nonstationarity. Accordingly, all the variables were prewhitened by regression on long-term trends and seasonal splines prior to CCF computation, and the same detrended series were used as inputs to the VAR model for Granger causality testing.

3.2. Cross-correlation function (CCF)

CCF analysis revealed significant lagged cross-correlations between all four meteorological predictors and DHF incidence (Figure 2; significance threshold: ± 0.046). As shown by Figure 2, the mean temperature exhibited its strongest positive cross-correlation at lag 11 days ($r=0.06$), with significant correlations at lags 0, 8, 9, and 10. The log-transformed rainfall was significantly positively correlated at a lag of seven days ($r=0.06$), with a secondary significant correlation at a lag of 27 days. The seven-day lag identified for rainfall has biological plausibility, aligning with the approximate

duration of the *Ae. aegypti* aquatic life stage, the period during which rainfall-induced expansion of standing water habitats translates into an increasing larval population prior to adult emergence.

For relative humidity, a statistically significant negative contemporaneous cross-correlation was observed ($r=0.05$ at lag 0), indicating that acutely elevated humidity on a given day was associated with reduced DHF case counts. The peak positive cross-correlation, however, emerged at the distal lag of 27 days ($r=0.05$), indicating that immediate high humidity may dampen outdoor human activity or transiently suppress vector behavior, whereas sustained humidity elevation over subsequent weeks favors vector longevity and facilitates the completion of the dengue virus extrinsic incubation period. The wind speed was positively correlated at lags of 9 and 23 days (peak $r=0.06$ at lag 23). This delayed positive association may reflect the wind-facilitated dispersal of adult mosquitoes to new human populations, which is consistent with the findings of vector dispersal studies in tropical urban settings. The presence of significant correlations extending to a lag of 27 days across multiple predictors collectively supports the specification of a 28-day maximum lag window in the DLNM.

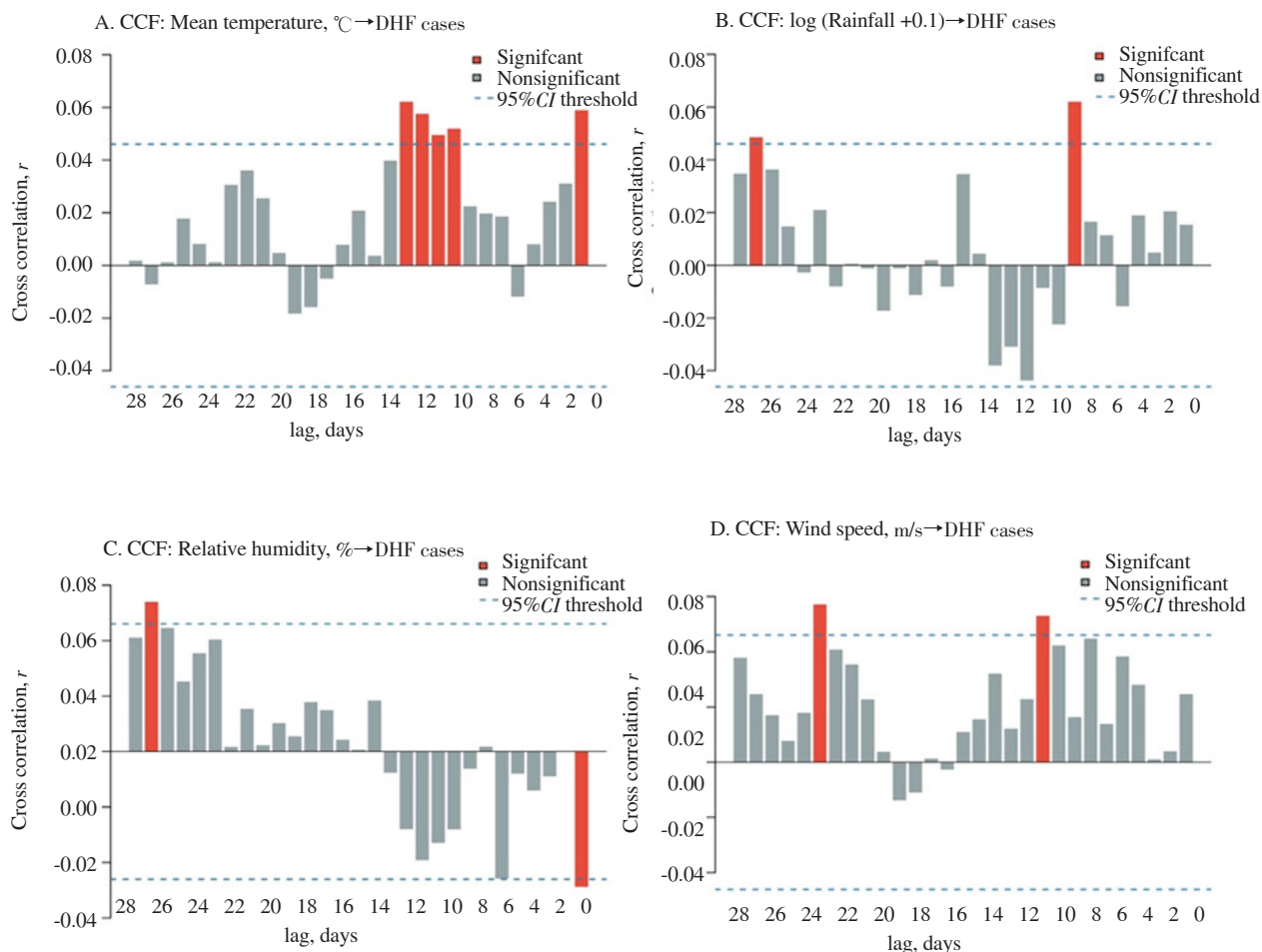


Figure 2. Cross-correlation between the detrended meteorological predictors and dengue hemorrhagic fever cases (lag of 0–28 days).

Table 1. Unidirectional temporal relationship by Granger causality test.

Causal direction	F-statistic	df	P-value
Temperature → DHF	2.310	28/8 840	<0.001
log (Rainfall) → DHF	1.635	28/8 840	0.02
Relative humidity → DHF	8.620	28/8 840	<0.001
Wind speed → DHF	3.560	28/8 840	<0.001
DHF → all climate (reverse)	1.135	—	0.28

df=degrees of freedom. DHF: dengue hemorrhagic fever.

Table 2. Sensitivity analysis.

Model specification	QAIC	Deviance explained (%)	Quasi-dispersion
df_trend = 6 (sensitivity)	4060.77	51.82	-
df_trend = 8 (final model)	3984.23	52.26	1.274
df_trend = 10 (sensitivity)	3994.18	52.89	-

3.3. Granger causality analysis

Granger causality tests confirmed that all four meteorological predictors, namely mean temperature, rainfall, relative humidity, and wind speed, significantly preceded DHF incidence in a VAR model with an optimal lag of $P=7$ (Table 1). Based on Table 1, relative humidity exhibited the strongest forward Granger causality ($F=8.62$, $df=28/8840$, $P<0.001$), followed by wind speed ($F=3.56$, $P<0.001$), mean temperature ($F=2.31$, $P<0.001$), and log-transformed rainfall ($F=1.64$, $P=0.02$).

The omnibus reverse causality test, which evaluates whether DHF case counts cause the meteorological predictors, was not statistically significant ($F=1.14$, $P=0.28$). This omnibus test was conducted as a joint test across all four meteorological predictors simultaneously within the VAR system, rather than as four separate individual reverse tests. These results confirm a unidirectional temporal relationship running from meteorological predictors to DHF incidence.

3.4. DLNM Model Fit and sensitivity analysis

The final quasi-Poisson DLNM ($df_trend=8$) explained 52.26% of the null deviance (Quasi-Akaike Information Criterion/QAIC = 3984.23; quasi-dispersion = 1.274; Pearson $\chi^2/df=1.274$). Sensitivity analyses across alternative trend spline specifications confirmed that $df_trend = 8$ produced the lowest QAIC among all the candidate models (Table 2), reflecting the most favorable balance between goodness-of-fit and model parsimony. A quasi-dispersion estimate of 1.274 indicated mild overdispersion in the outcome data, which was adequately addressed through the quasi-Poisson distribution family.

3.5. Exposure–Lag–Response associations

3.5.1. Mean temperature

The cumulative exposure-response curve for mean temperature demonstrated a nonlinear, J-shaped association with DHF incidence

(Table 3; Figure 3A). Temperatures below the median reference of 27.60 °C showed a generally protective pattern, though not uniformly significant across the lower range (5th percentile: 25.60 °C). However, at the 10th percentile [26.10 °C; RR 0.66 (95% CI 0.47–0.92)], and at the 25th percentile (26.80 °C; RR 0.64 (95% CI 0.48–0.84)] was found significant. Conversely, temperatures above the median were associated with substantially increased risk, namely, at the 75th percentile [28.10 °C; RR 1.41 (95% CI 1.19–1.67)], at the 90th percentile (28.60 °C; RR 1.89 (95% CI 1.41–2.52)], and at the 95th percentile (28.90 °C; RR 2.13 (95% CI 1.43–3.19)]. Across the full observed temperature range, the maximum cumulative RR reached 4.285 at 23.70 °C, although the associated confidence intervals were wide, reflecting data sparsity at extreme temperatures. The minimum cumulative RR of 0.62 (95% CI 0.45–0.85) was identified at 26.46 °C, interpolated from the continuous crosspred exposure-response surface at the point of minimum predicted risk, a value falling between P25 (26.80 °C) and P10 (26.10 °C) of the observed temperature distribution. At the peak CCF lag of 11 days, the lag-specific RR at P90 temperature was 1.02 (95% CI 1.01–1.04).

3.5.2. Daily rainfall

Among all the meteorological predictors, log-transformed daily rainfall exhibited the strongest and most meaningful cumulative association with DHF incidence (Table 3; Figure 3B). The exposure-response relationship for rainfall was nonlinear, with DHF risk increasing at values above the median reference point (log-scale of 0.74, ≈ 2.00 mm/day). At the 75th percentile (log- $RR=2.38$, ≈ 10.5 mm/day), the cumulative RR was 3.94 (95% CI 2.28–6.80); at the 90th percentile (log- $RR=3.38$, ≈ 29.3 mm/day), the RR was 4.23 (95% CI 2.10–8.52); and at the 95th percentile (log- $RR=3.89$, 48.7 mm/day), the RR was 3.67 (95% CI 1.56–8.63). On the other hands, below the reference, the 5th, 10th and 25th percentile values (log- $RR=-2.303$; $RR=1.84$, 95% CI 0.97–3.47) corresponded to near-zero rainfall days. Although the point estimate suggested an elevated risk to the median, but it is not significant. The maximum cumulative RR of 4.377 (95% CI 2.347–8.165) was observed at log- $RR = 2.984$ (≈ 19.7 mm/day). At the peak CCF lag of 7 days, the lag-specific RR at the 90th percentile rainfall was 1.07 (95% CI 1.04–1.10).

3.5.3. Relative humidity

The cumulative exposure-response relationship for relative humidity was complex and nonmonotonic, a pattern consistent with the biphasic temporal dynamics previously identified in the CCF analysis (Table 3; Figure 3C). Although, none of the percentile-specific cumulative *RR* estimates reach significant at the 5% level, namely at the 5th percentile [77.00%; *RR* 0.67 (95% *CI* 0.41-1.17)]; at the 10th percentile [78.00%; *RR* 0.86 (95% *CI* 0.56-1.29)]; at the 25th percentile [81.00%; *RR* 1.08 (95% *CI* 0.83-1.39)], at the 75th percentile [86.00%; *RR* 0.82 (95% *CI* 0.57-1.17)]; at the 90th percentile [88.00%; *RR* 0.85 (95% *CI* 0.50-1.46)], and at the 95th percentile [89.00%; *RR* 0.91 (95% *CI* 0.46-1.80)].

Table 3. Cumulative relative risk (*RR*) of dengue hemorrhagic fever incidence at key percentiles of each meteorological predictors (lag 0-28 days).

Percentile	Value	Cumulative <i>RR</i> (95% <i>CI</i>)
Mean temperature, °C (Ref.: 27.60 °C)		
P5	25.60	0.80 (0.50-1.25)
P10	26.10	0.66 (0.47-0.92)*
P25	26.80	0.64 (0.48-0.84)*
P50 (ref.)	27.60	1
P75	28.10	1.41 (1.19-1.67)*
P90	28.60	1.89 (1.41-2.52)*
P95	28.90	2.13 (1.43-3.19)*
log (Rainfall + 0.1) (Ref.: 0.74 log-mm: approximately 2.00 mm)		
P5 ^a	-2.303	1.84 (0.97-3.47)
P10 ^a	-2.303	1.84 (0.97-3.47)
P25 ^a	-2.303	1.84 (0.97-3.47)
P50 (ref.)	0.742	1
P75	2.375	3.94 (2.28-6.80)*
P90	3.381	4.23 (2.10-8.52)*
P95	3.885	3.67 (1.56-8.63)*
Relative humidity, % (Ref.: 83.00%)		
P5	77.00	0.70 (0.41-1.17)
P10	78.00	0.86 (0.56-1.29)
P25	81.00	1.08 (0.83-1.39)
P50 (ref.)	83.00	1
P75	86.00	0.82 (0.57-1.17)
P90	88.00	0.85 (0.50-1.46)
P95	89.00	0.91 (0.46-1.80)
Wind speed, m/s, (Ref.: 2.00 m/s)		
P5 ^b	1.00	0.75 (0.50-1.13)
P10 ^b	1.00	0.75 (0.50-1.13)
P25 ^b	1.00	0.75 (0.50-1.13)
P50 (ref.)	2.00	1
P75 ^c	2.00	1 (-)
P90 ^d	3.00	1.73 (1.25-2.39)*
P95 ^d	3.00	1.73 (1.25-2.39)*

**P* < 0.05 ; Identical adjacent value reflects real data features: a) ~ 25% of days had zero/near zero rainfall, b-d) wind speed was measured at coarse.

3.5.4. Wind speed

Wind speed, as shown in Table 3 and Figure 3D, exhibited a nonlinear cumulative association with DHF incidence, with notable clustering of values at 1.00 m/s (5th-25th percentiles) and 2.00 m/s (50th-75th percentiles), reflecting the discrete nature of the wind speed measurement in the dataset.

At the 5th-25th percentiles (1.00 m/s), the cumulative *RR* was 0.75 (95% *CI* 0.50-1.13), indicating a modest protective effect at low wind speeds although it is not statistically significant. At the 90th-95th percentile (3.00 m/s), *RR* was 1.73 (95% *CI* 1.25-2.39). This pattern is indicative of elevated DHF risk at higher wind speeds, potentially attributable to wind-facilitated dispersal or *Aedes* mosquitoes into new susceptible host populations. The maximum cumulative *RR* of 4.42 (95% *CI* 0.53-36.79) occurred at the extreme value of 5.00 m/s, although it is not statistically significant, reflecting the sparse number of observations. At the peak CCF lag of 23 days, the lag-specific *RR* at the 90th percentile wind speed (3.00 m/s) was 1.03 (95% *CI* 1.01-1.04).

To complement the cumulative exposure-response analyses, lag-specific relative risks at the 90th percentile of each meteorological predictor were extracted at the peak lag identified from the CCF analysis as shown in Figure 2.

At the peak CCF lag of 11 days, the mean temperature at the 90th percentile (28.60 °C) was associated with a lag-specific *RR* of 1.024 (95% *CI* 1.008-1.039), representing a statistically significant 2.4% increase in daily DHF risk at this lag (Figure 4A). The lag-specific curve gradually increased from lag 0, reaching a modest peak between lags 11 and 13 days, and subsequently stabilizing. The log-transformed rainfall at the 90th percentile (log=3.381; approximately 29 mm/day) produced the strongest lag-specific association, with an *RR* of 1.07 (95% *CI* 1.04-1.10) at the peak CCF lag of 7 days (Figure 4B). The lag-specific curve remained elevated above unity from lag 0 through approximately lag 20, declining progressively toward the null by lag 28, where a pattern suggested that the impact of a high-rainfall event on DHF risk was most acute within the first week and diminished steadily thereafter.

Relative humidity at the 90th percentile (88.00%) exhibited a distinct temporal trajectory, with lag-specific *RR* values at or below unity throughout the early lag window (lags 0-15), before rising progressively to an *RR* of 1.04 (95% *CI* 0.99-1.08) at the peak CCF lag of 27 days (Figure 4C). On the other hand, the wind speed at the 90th percentile (3.00 m/s) showed a gradually increasing lag-specific *RR* over the observation window, reaching *RR* 1.03 (95% *CI* 1.01-1.04) at the peak CCF lag of 23 days (Figure 4D). The lag-specific curve remained close to unity at early lags before rising steadily beyond lag 15.

Table 4. Population attributable fraction and attributable number of dengue hemorrhagic fever cases by meteorological predictor in Cilacap Regency.

Variable	Direction	Attributable number (AN)	Attributable fraction (AF) (%)
Mean temperature	Risk factor (+)	176.6	6.22
log(Rainfall)	Risk factor (+)	783.5	27.58
Relative humidity	Protective (-)	-409.0	-14.40
Wind speed	Protective (-)	-95.7	-3.37

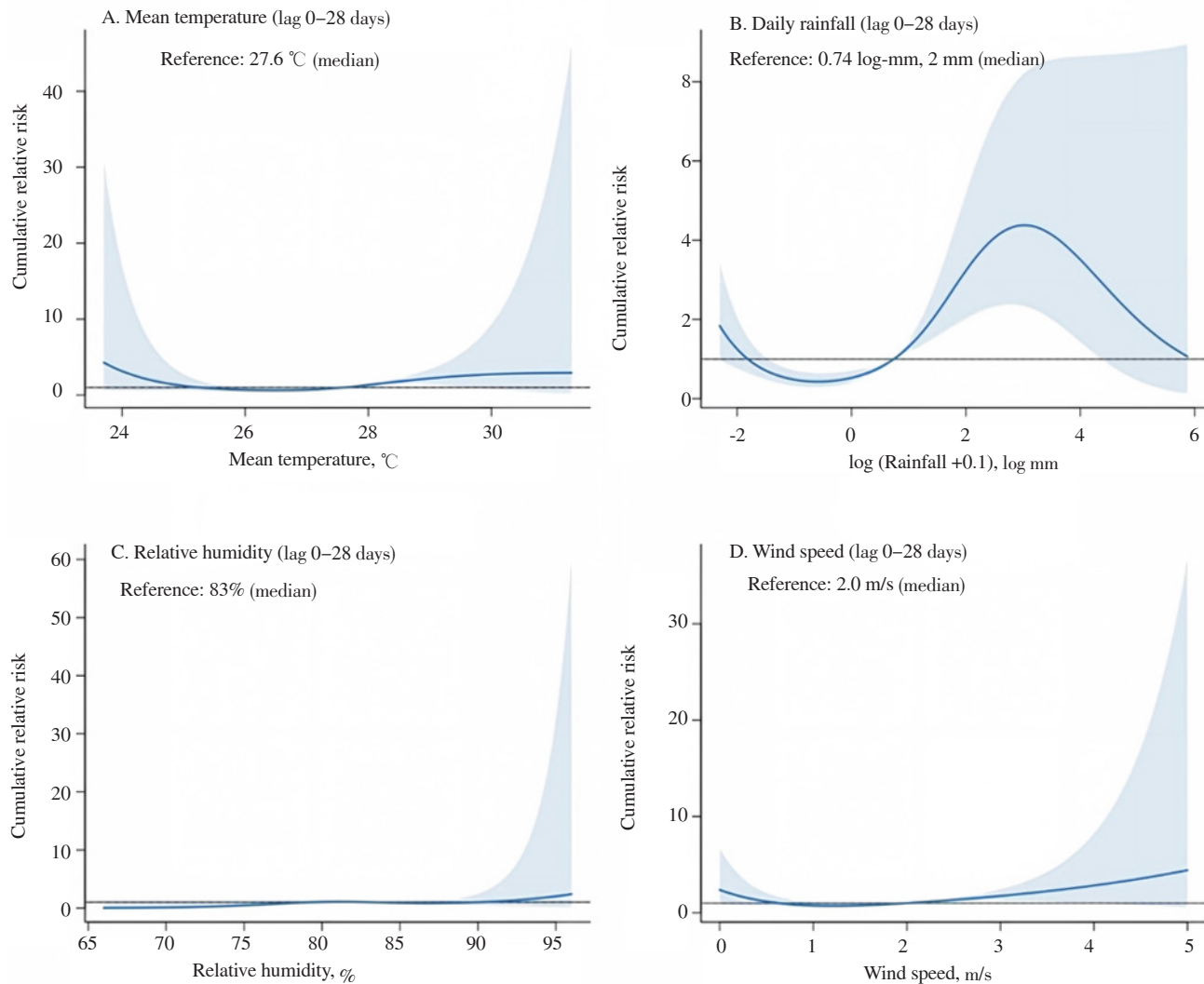


Figure 3. Cumulative exposure-response curves from the Distributed Lag Nonlinear Model (lag of 0–28 days).

3.6. Population attributable fraction

Table 4 shows the population attributable fraction and attributable number of DHF cases by meteorological prediction. Rainfall was the dominant meteorological contributor to the DHF burden in Cilacap, with an attributable fraction (AF) of 27.58% [analytic number (AN)=783.5 cases]. The mean temperature contributed an AF of 6.22% (AN=176.6 cases). These two risk factors accounted for approximately 33.8% of the total DHF burden over the study period. Relative humidity and wind speed exhibited protective fractions of -14.40% (AN=-409.0) and -3.37% (AN=-95.7), respectively. These negative AF values indicate that, relative to the median reference conditions, the observed distributions of humidity and wind speed in Cilacap were associated with a net suppression of DHF cases over the 28 day lag window.

These attributable fractions are derived by integrating cumulative RR curves that include ranges without statistically significant point-level association. Therefore, this finding should be interpreted

as directional, model-based summaries rather than statistically confirmed effects at every point along the exposure distribution.

4. Discussion

This study characterized the nonlinear, lagged associations between daily meteorological exposures and dengue hemorrhagic fever (DHF) incidence in Cilacap Regency, Central Java, Indonesia, during 2021–2025. The principal findings of this study were as follows, namely: 1) Daily rainfall was the dominant meteorological predictor of DHF in Cilacap, 2) Mean temperature exhibited a J-shaped nonlinear association with DHF incidence, with markedly elevated risk above approximately 28 °C, 3) Relative humidity and wind speed exerted net protective effects on DHF burden, though with substantial uncertainty at the individual percentile level, and 4) Granger causality testing confirmed unidirectional predictive relationships from all four meteorological predictors to DHF incidence.

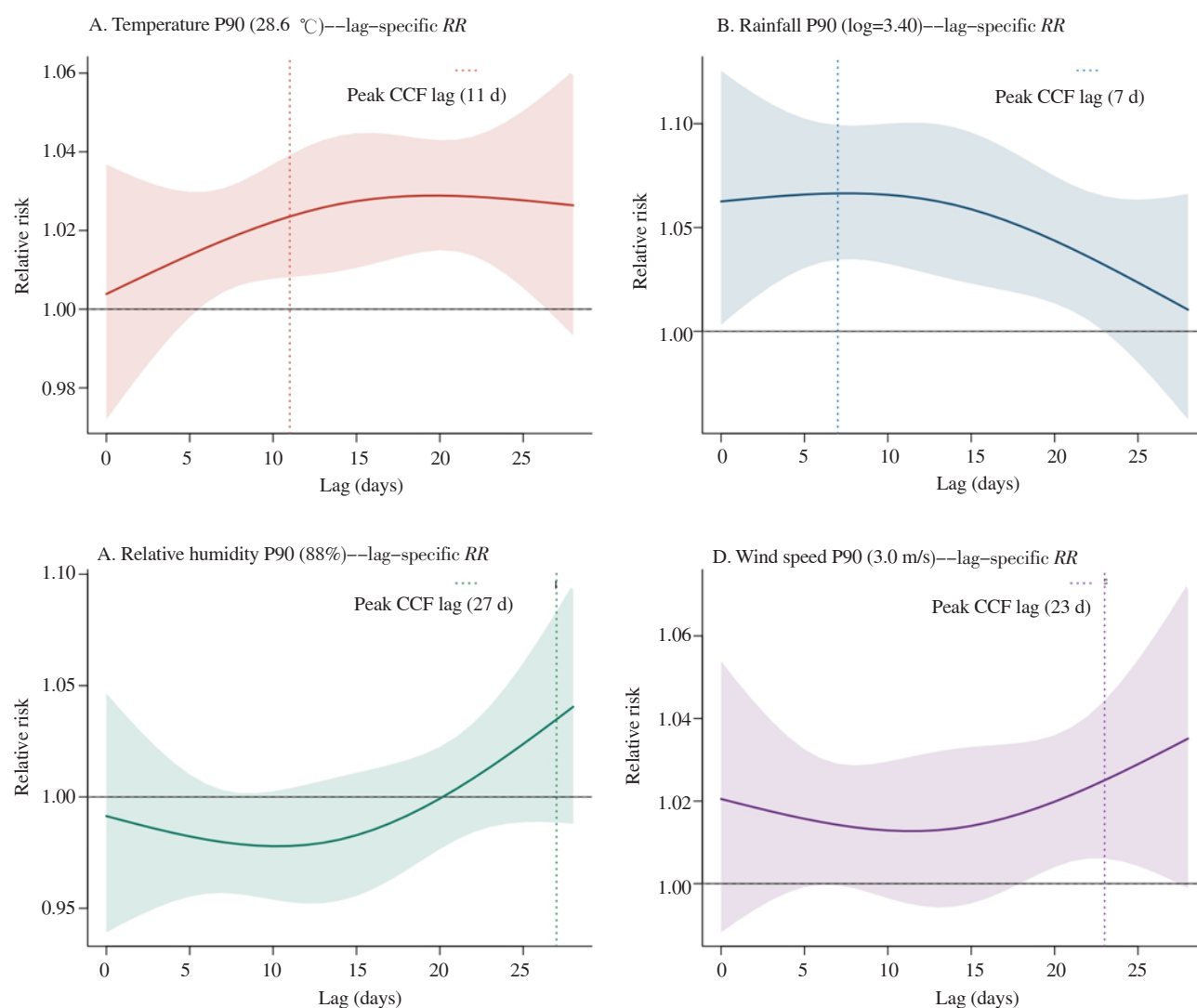


Figure 4. Lag-specific RR at P90 exposure. RR: relative risk, P90: 90th percentile.

The J-shaped cumulative exposure-response curve for mean temperature, with a protective nadir below the median and a progressive risk elevation at higher temperatures, is consistent with the known thermal biology of *Ae. aegypti*. Based on previous study, laboratory evidence from Mordecai *et al.*[26] indicates that DENV (Dengue virus) transmission by *Ae. aegypti* is optimal between 26 °C and 29 °C, and that temperature accelerates larval development rates, shortens the gonotrophic cycle, and reduces the extrinsic incubation period of DENV within the vector[27]. The protective association observed at temperatures below 27 °C is biologically coherent within the context of Cilacap's thermal range, aligning with established thresholds below which *Aedes* mosquito development slows and vector competence is reduced[28,29].

The 11-day peak CCF lag for temperature has biological plausibility, reflecting the cumulative duration of the *Ae. aegypti* aquatic developmental stage[30], the subsequent adult maturation period, and the onset of active biting activity peaks in the morning and afternoon[31]. The lag-specific RR at lag 11 days and the 90th percentile temperature (28.6 °C) was 1.024 (95% CI 1.01-

1.04), indicating a modest but statistically significant day-specific elevation in DHF risk at this biologically relevant lag. This delayed temperature signal is consistent from Wibawa *et al.*[32], where extreme high temperature significantly increased dengue risk in Semarang. Similarly, Polrob *et al.*[29] documented pronounced spatial and temporal heterogeneity in climate-dengue associations across Bangkok's urban zones.

The wide confidence intervals observed at extreme temperature values reflect data sparsity at the distributional tails, with fewer than 3 observation days recording temperature below 24 °C and warrant caution in interpretation. This data sparsity is resulting in wide confidence intervals and limited spline support at this distributional extreme. Future studies with larger temporal coverage or multisite designs would benefit from penalized spline or meta-analytical pooling approaches to improve precision.

The identification of daily rainfall as the dominant meteorological determinant of DHF incidence in Cilacap is consistent with the established breeding ecology of *Ae. aegypti*. Rainfall creates and replenishes standing water in peridomestic containers, which

represent the principal oviposition sites for *Ae. aegypti* in urban and peri-urban settings, per WHO guidance on vector breeding ecology[33]. The observed 7-day lag to peak correlation, closely aligns with the duration of the *Ae. aegypti* aquatic life stage under tropical conditions, after which newly emerged adult females initiate blood-seeking behavior and begin to contribute to transmission.

A notable feature of the exposure-response curve for rainfall was the elevated cumulative risk observed at the lower end of the distribution. This pattern is consistent with Nuraini *et al.*[34], who reported in a Central Java, dengue model that both anomalously wet and dry conditions were associated with elevated dengue risk, and is broadly consistent with the wider pattern of climate-dengue sensitivity previously reported by Wibawa *et al.*[32]. The elevated risk at near-zero rainfall likely reflects a combination of reduced mosquito egg flushing during dry condition, increased household water storage, and increased concentration of larval breeding in residual water containers.

The secondary significant CCF correlation at a lag of 27 days for rainfall, together with a slight decline in cumulative risk at highest percentile relative to the 90th percentile, suggests potential nonmonotonic dynamics at extreme rainfall values, possibly reflecting a flushing effect at very high precipitation intensities that removes larval habitats and suppresses vector populations[35]. The cumulative *RR* of 4.23 observed in Cilacap for P90 rainfall in the present study falls within this range, suggesting that Cilacap's rainfall-DHF relationship is broadly representative of high-burden coastal Java provinces. Li *et al.*[36], studying Coastal Southeastern China, found that dengue incidence was associated with hydrological condition across different lags, with effect of modification by urbanization, income, green space, and health resources.

The exposure-response pattern for relative humidity, characterized by a significant negative contemporaneous CCF and a delayed positive peak at lag 27 days, warrants careful interpretation. The acute inverse association between high daily humidity and DHF incidence at lag 0 may reflect a suppression of human outdoor activity and exposure to mosquito bites on days of extreme humidity or rainfall, thereby reducing effective contact between the human host and the vector. However, the delayed positive association at lag 27 is consistent with the role of sustained humidity in prolonging *Ae. aegypti* adult longevity and maintaining vector competence during the extrinsic incubation period of DENV. Courate *et al.*[23] demonstrated that the survival of *Ae. aegypti* is substantially enhanced when the relative humidity is above 70%-80%. Additionally, Wu *et al.*[37] identified a similar humidity pattern, in which humidity was positively associated with dengue above a threshold at longer lags.

Wind speed demonstrated a nonlinear cumulative association with DHF incidence, with a protective effect at lower speeds and elevated risk at higher speeds. The peak CCF lag of 23 days was the most distal among all four predictors. Wind-assisted passive dispersal of adult *Ae. aegypti* into new peridomestic environments could introduce the vector to previously unexposed host populations, where Marcantonio *et al.*[38] estimated that adult *Ae. aegypti* can disperse on average over 200 meters, influenced by wind speed and

direction. Wind speed and sun exposure influences the microclimatic conditions within outdoor breeding containers, where higher wind speeds can accelerate evaporation, concentrate larval nutrients, and alter water temperature in ways that modify larval development trajectories[39].

The nonlinear and spatially heterogeneous association for humidity and wind speed associations reported in Bangkok share structural resemblance to the patterns identified here, although the lag structures differed considerably, where a discrepancy is attributable in part to differences in temporal resolution, urban morphology, and local vector ecology[29].

The confirmation of significant Granger causality from all four meteorological predictors to DHF incidence addresses a fundamental limitation of many ecological time-series studies of climate and infectious diseases. It should be emphasized that Granger causality establishes temporal predictive precedence. Notably, the relative ranking of Granger causality strengths did not correspond to the ranking of attributable fraction, with the relative humidity showed the strongest Granger-causal signal, yet rainfall contributed the largest attributable fraction. This divergence highlights an important distinction between confirming that a predictor temporally precedes DHF incidence and quantifying the magnitude of its contribution to disease burden.

The interannual variation in DHF burden is consistent with the cyclical epidemiological dynamics of dengue in Indonesia. At the national level, multiannual outbreak peaks coincided with strong El Niño events, with Djaafara *et al.*[40] reporting the mean dengue incidence during strong El Niño years was higher than that in other years. The relatively low burden observed in Cilacap, following the high-incidence years of 2021 and 2022, was likely catalyzed by health official intervention to tackling DHF incidence in Cilacap, such as surveillance and mosquito breeding site control program.

The findings of this study have several actionable implications for DHF surveillance and vector control policies in Cilacap Regency. The identification of a 7-day lag between rainfall and DHF incidence provides a biologically grounded early warning window. Intensification of rainfall-triggered vector control could plausibly interrupt transmission at a critical point in the vector development cycle. This aligns with the World Health Organization's recommendations for environmental management as the primary vector control strategy[33]. The identified temperature threshold of approximately 28 °C has direct implications for climate change projections in Cilacap, underscoring the urgency of integrating climate projections into long-term dengue control planning for Cilacap Regency.

The combined meteorological attribution of rainfall and temperature, roughly one-third of the DHF burden in Cilacap, implies substantial share of cases may be attributable to above median meteorological condition. These attributable fraction estimates carry substantial uncertainty, including the absence of formal confidence interval, and should not be interpreted as direct causal population-level estimates, they provide a useful order-of-magnitude framework for the potential impact of meteorologically-informed vector control

intensification relative to climate-independent baseline surveillance.

This study is subject to several limitations, as follows: 1) As an ecological time-series study, the analysis should be interpreted with caution due to the potential for ecological fallacy, in which the meteorological effects estimated at the population level may not accurately reflect individual-level exposure-response relationships, and unmeasured confounders that is not fully addressed. 2) The attributable fraction estimates were computed *via* interpolation of the cumulative relative risk surface from the crosspred object, where future studies should incorporate parametric bootstrap simulations to generate AF confidence intervals. 3) The study period encompasses the years of the COVID-19 pandemic, where movement restrictions and altered healthcare-seeking behavior may have affected both DHF case ascertainment and the human-vector contact patterns. Therefore, a comparative analysis of pre- and post-pandemic meteorological-DHF associations would be valuable in future work. 4) Rainfall exhibited a higher proportion of missing data than other meteorological predictor, which were address using linear interpolation. Therefore, this condition could influence the magnitude of estimated rainfall exposure - response relationship. 5) Residual autocorrelation, though substantially reduced by the seasonal spline and autoregressive terms, remained formally significant (Ljung-Box=80.26, $P<0.001$), where it is likely a function of the large sample size rather than model misspecification, given ACF values below 0.09 at lags 2-7.

In conclusion, this study provides daily quantification of the nonlinear, lagged meteorological determinants of DHF incidence in Cilacap Regency, Indonesia. This study confirmed the unidirectional temporal precedence of all the meteorological predictors to DHF incidence. Additionally, rainfall emerged as the meteorological predictor contributing most to DHF burden (AF=27.58%), with a biologically coherent 7-day lag and a nonlinear exposure-response relationship peaking at 20-30 mm/day. The mean temperature demonstrated a J-shaped nonlinear association with DHF risk, with a threshold in the 27-28 °C range above which the risk increased sharply. Relative humidity and wind speed exerted complex, nonlinear, time-varying effects with net protective attributable fractions across the observed exposure distributions.

Combining vector control program and early warning system using meteorological predictor would benefit health office of Cilacap to efficiently and effectively reduce the DHF outbreak in Cilacap.

Conflict of interest statement

Authors declare that there is no conflict of interest

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Authors' contributions

K.A: Concepts, design, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript review. S.M.D.P: Concept, literature search, data analysis, manuscript preparation, editing, and review. Both D.H.P and Y.S.V: Manuscript preparataion, editing, and review. I.M.D.M.: Concepts, design, data analysis, statistical analysis, manuscript preparation, editing, and review. D.S.S.R. supervised the project.

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