Lipids in Health and Disease

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# Association between monocyte-high-density lipoprotein cholesterol ratio and mortality in a population with asthma: a cohort study

Qin Zhang[2†], Jing Xia[3†], Rongjuan Zhuang[4†], Jun Wen[4*] and Changfen Wang[1*]

## Abstract

**Background** The monocyte-high-density lipoprotein cholesterol ratio (MHR) serves as an integrated indicator of the pro-inflammatory role of monocytes and anti-inflammatory properties of high-density lipoprotein cholesterol (HDL-C). Research has shown that the MHR is associated with the onset and prognosis of some diseases. However, no study has examined the link between the MHR and prognosis of populations with asthma.

**Methods** This study included data from 2,023 participants with asthma from the National Health and Nutrition Examination Survey (NHANES). This survey applied various statistical models, such as Cox proportional hazards, restricted cubic spline (RCS), threshold effects analysis (TEA), Kaplan–Meier survival analysis, and survival area plots, to assess the correlation between the MHR and mortality in participants with asthma.

**Results** According to the Cox hazard models, the MHR and mortality were positively correlated (hazard ratio: 1.93, 95% confidence interval: 1.20–3.11). Additionally, the RCS and TEA demonstrated a positive and linear relationship between the MHR and mortality. Participants with asthma who had a decreased MHR had better survival, compared with those who had an elevated MHR, as per the Kaplan–Meier survival analysis and survival area plots.

**Conclusions** This longitudinal investigation indicated that an increased MHR was associated with elevated mortality in individuals with asthma. Therefore, the MHR may serve as an independent biomarker for predicting the prognosis of individuals with asthma.

**Keywords** Monocyte-high-density lipoprotein cholesterol ratio, High-density lipoprotein cholesterol, Asthma, Mortality, Survival area plot

†Qin Zhang, Jing Xia and Rongjuan Zhuang contributed equally to this work, sharing the first author.

*Correspondence:
Jun Wen
wencej@stu.cqmu.edu.cn
Changfen Wang
15885973413@163.com
[1]Department of Cardiology, People's Hospital of Qianxinan Prefecture, Guizhou Province, China
[2]Department of Cardiology, Xi Chang People's Hospital, Xi Chang, Sichuan Province, China
[3]Department of Respiratory and Critical Care Medicine, The Third Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China
[4]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China

## Introduction

Asthma is a chronic respiratory disease characterized by inflammation, wheezing, and coughing [1]. Owing to ongoing societal advancements, the incidence and socioeconomic impact of asthma are increasing annually. In 2019, more than 200 million people worldwide suffered from asthma, and 455,000 of them died [2]. Early death and reduced quality of life due to asthma impose a significant economic burden [3]. A Canadian study revealed that the financial burden of biological therapy is heavy for patients with difficult-to-control asthma, and the cost of treatment increases sharply for patients with extremely severe and difficult-to-control asthma [4].

Asthma is a multifaceted, heterogeneous condition characterized by diverse pathophysiological elements arising from various inflammatory pathways [5, 6]. Previous research has highlighted the contribution of both localized and systemic inflammatory reactions to asthma progression [7]. Studies have demonstrated the complex interactions between monocyte and high-density lipoprotein cholesterol (HDL-C) with oxidative stress, inflammatory responses, and lipid metabolism [8], all of which are crucial for the development of asthma. Monocytes migrate to sites of inflammation, thereby exacerbating oxidative stress [9]. Concurrently, these cells can differentiate into macrophages, which play a vital role in maintaining chronic inflammation in asthma [10]. Macrophages discharge large amounts of inflammatory mediators that engage and stimulate more immune cells, thereby sustaining the cycles of inflammation. Additionally, research has indicated that markers related to monocytes, notably the monocyte-to-lymphocyte ratio (MLR), derived from monocyte and lymphocyte counts, are correlated with both the risk of developing asthma and severity of asthma. Thus, they can potentially serve as predictors of clinical outcomes in individuals suffering from asthma [11, 12]. In contrast, HDL-C possesses anti-oxidant, anti-thrombotic, and anti-inflammatory properties [13]. Further, it suppresses inflammation by inhibiting macrophage migration [14]. The correlation between HDL-C levels and asthma has attracted significant research attention. Notably, a previous study revealed a link between HDL-C levels and the risk of developing asthma [15]. In addition, the development of novel hematological parameters associated with HDL-C, such as the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), has emerged as a novel approach for predicting the prevalence of asthma. Consequently, monocytes and HDL-C show potential as powerful biomarkers for assessing disease severity in patients with asthma.

The monocyte-high-density lipoprotein cholesterol ratio (MHR) is derived by dividing the monocyte count by the HDL-C level and reflects the balance between inflammation and anti-inflammation. Recently, this metric has been proven to be a powerful tool for risk stratification and prognostic assessment of cardiovascular disease [16, 17]. However, the link between the MHR and mortality rate in patients with asthma has not been definitively established. This gap underscores the urgent need for thorough and multidimensional research on the potential predictive value of the MHR for asthma-related health outcomes. Such studies are crucial to refine our understanding and guide future therapeutic strategies aimed at mitigating asthma-related mortality. The relationship between the MHR and mortality in a population with asthma was examined using the National Health and Nutrition Examination Survey (NHANES) data.

## Materials and methods

### Study data and population

The research was undertaken by applying data from the NHANES database of the Centers for Disease Control and Prevention (CDC). Project approval was approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS). An informed permission form was filled out by each participant, attesting to their understanding of and consent to the experiment. All database data was anonymized. Once populations without follow-up data, asthma, MHR, or covariates had been removed, this research finally contained 2023 asthmatics (Fig. 1).

### Main research variables

The MHR was treated as the independent variable in this investigation, whereas mortality was the outcome variable. The MHR was calculated as follows: monocyte count (1,000 cells/uL)/HDL-C level (mmol/L). This study used mortality data until December 31, 2019 to determine the follow-up status of the population. Further information regarding the matching approach is provided by the NCHS. Death status was determined based on the International Classification of Diseases, tenth revision.

### Other variables

To lessen the influence of confounding variables, a number of covariates were incorporated into the research. The covariates contained in this research were sex, race, age, smoking, alcohol, education, marriage, body mass index (BMI), hypertension, diabetes, cardiovascular disorder (CVD), other chronic respiratory diseases (CRD), cancer, hay fever, systemic immune inflammation index (SII), systemic inflammation response index (SIRI), cholesterol, and triglyceride. The standard medical questionnaire was employed in this investigation to ascertain the asthmatic individual. Has a physician diagnosed you with asthma? Positive responses indicated asthma.

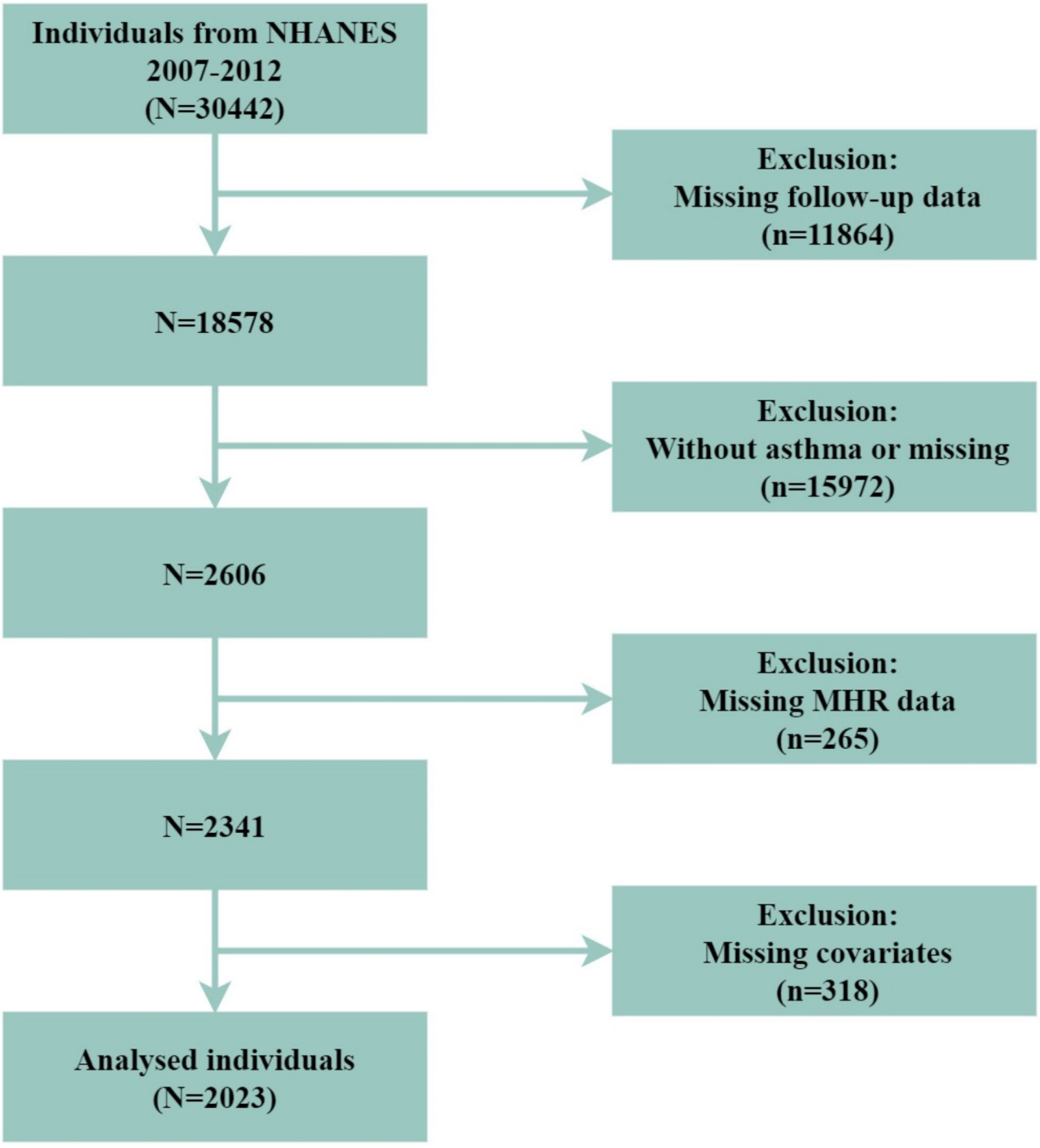


**Fig. 1** Flow chart for screening the research population

### Statistical analysis

For categorical data, the *P*-value was ascertained using the chi-square test. The Kruskal-Wallis rank-sum test was implemented to compute the *P*-value for continuous variables. Initially, this investigation employed three Cox regression models to assess the correlation of MHR with the death risk in asthmatics. Multivariate Cox regression models considered covariates that met any of these conditions. A covariate that could change the effect estimate by at least 10% was added, selected based on previous research and database limitations. Afterwards, restricted cubic spline (RCS) and threshold effect analysis (TEA) based on models that adjust for all covariates were applied to further quantify the relationship between

MHR and the death risk. This investigation also applied the Kaplan-Meier survival analysis and survival area plot to evaluate the impact of MHR on the survival status during the follow-up period. This research also addressed the missing covariates in this study through multiple imputations, with the proportion of each missing covariate being less than 10%. Finally, conduct sensitivity analyses of the primary findings using the data generated through multiple imputations. This research employed corresponding sample weights to handle the intricate sampling method of the NHANES. *P-value* < 0.05 was considered statistically significant, and this investigation used R 4.4.1 for all statistical analyses.

## Results

### Baseline characteristics

2023 asthmatic people (850 men and 1173 women) were included in this research, and the baseline characteristics were compared according to MHR tertile groups. The mean follow-up duration for participants was 117 months. Statistical differences were observed in the distributions of sex, race, education, BMI, smoking, hypertension, diabetes, CVD, SII, SIRI, cholesterol, and triglyceride. The larger the MHR, the higher the likelihood of death in asthma patients (Table 1).

### Association between the MHR and mortality

This study applied three Cox regression models to investigate the link between MHR with the death risk in asthmatics (Table 2). Among three Cox models, the rise in MHR was linked to elevated mortality in asthmatic individuals. The risk of mortality elevated by 93% for every additional unit of MHR in Model III, after all confounders were adjusted. In addition, trend tests of the relationship of MHR with death risk were statistically significant in Models I and II but not in Model III. Furthermore, the relationship between MHR and asthma mortality risk was further quantified by applying the RCS (Fig. 2) and TEA (Table 3). MHR and mortality in asthmatic populations were linearly positively correlated, according to the findings of both RCS and TEA.

### Survival curve

Additionally, this investigation applied grouped (Fig. 3) and continuous MHR (Fig. 4) to generate cumulative survival curves in order to assess the influence of MHR on the survival of asthmatic populations. The survival curves of grouped MHR and consecutive MHR both suggested that asthma populations with lower MHR had higher survival rates compared to those with higher MHR.

### Subgroup and sensitive analysis

In white women over 60 with hypertension, diabetes, CVD, and other CRD but without hay fever, the findings of the subgroup analysis proved a positive link between MHR with the probability of death(Table S1). After multiple imputations of all the missing confounding variables, the main outcomes from the imputed data were mostly the same as the previous results: MHR was linearly and positively linkedto the risk of death (Tables S2 and S3, Figure S1).

## Discussion

This longitudinal investigation is the first to investigate the association between the MHR and prognosis in patients with asthma. According to numerous statistical models, an increase in the MHR was linked to an elevated mortality risk in individuals with asthma. Both the RCS and TEA revealed a positive linear correlation between the MHR and mortality. These findings suggest that the MHR could function as an independent biomarker for predicting the prognosis of patients with asthma.

A range of cell types are implicated in the inflammatory process in patients with asthma, with prior studies concentrating predominantly on eosinophils, which are frequently used as hematological indicators of the onset and exacerbation of asthma [18, 19]. Contemporary research has increasingly acknowledged the utility of complete blood count (CBC) parameters and related inflammatory biomarkers in assessing the severity of asthma and identifying therapeutic interventions [20]. Neutrophils release a wide range of proinflammatory mediators that drive airway inflammation and play a crucial role in triggering acute exacerbation of asthma [21]. T helper 2 cells, a specific subtype of lymphocytes, are pivotal in the pathogenesis of asthma because they secrete cytokines that exacerbate respiratory inflammation, stimulate mucus generation, and induce bronchoconstriction [22]. Monocytes can initiate inflammation directly or differentiate into macrophages, which perpetuate the inflammatory cycle by releasing inflammatory mediators [10]. Monocytes regulate the recruitment and activation of eosinophils during lung inflammation by secreting cytokines and chemokines [23]. Notably, an abnormal monocyte differentiation process and heightened levels of monocyte-derived transforming growth factor beta 1 have been identified as markers of severe asthma [24]. The SII, calculated from CBC data, has proven to be a valuable predictor of mortality in individuals with chronic obstructive pulmonary disease (COPD) and asthma [25]. Additionally, an elevated MLR has been linked to increased inflammation and aggravated airway hyperresponsiveness, subsequently resulting in an increased risk of death in patients with asthma [11, 26]. Consistent with these observations, Ke et al. highlighted the MLR as an exceptionally reliable predictor of mortality in individuals with asthma [27].

**Table 1** Baseline characteristics of study populations based on MHR tertile groups

| | T1 (0.05–0.32) | T2 (0.32–0.48) | T3 (0.48–3.62) | *P* value |
|---|---|---|---|---|
| Sex (%) | | | | 0.0001 |
| Female | 71.54 | 60.40 | 46.12 | |
| Male | 28.46 | 39.60 | 53.88 | |
| Age (years) | 45.00 (31.00,59.00) | 43.00 (30.00,58.00) | 44.00 (30.00,58.00) | 0.2805 |
| Race (%) | | | | 0.0007 |
| Other Race populations | 14.77 | 17.66 | 15.35 | |
| White populations | 68.40 | 69.83 | 75.07 | |
| Black populations | 16.83 | 12.51 | 9.58 | |
| Education (%) | | | | 0.0203 |
| Less than high school | 15.47 | 17.01 | 20.13 | |
| High school | 20.41 | 20.68 | 25.74 | |
| More than high school | 64.12 | 62.31 | 54.13 | |
| Marriage (%) | | | | 0.9920 |
| Married | 48.61 | 49.67 | 49.56 | |
| Single | 43.49 | 41.97 | 41.89 | |
| Living with a partner | 7.90 | 8.36 | 8.55 | |
| BMI (kg/m2) | 26.10 (22.90,31.00) | 28.83 (24.50,33.80) | 30.80 (26.72,35.60) | 0.0001 |
| Alcohol intake (gm) | 12.82 ± 1.59 | 13.53 ± 1.72 | 9.69 ± 1.17 | 0.1182 |
| Smoking (%) | | | | 0.0001 |
| No | 58.20 | 49.95 | 42.13 | |
| Yes | 41.80 | 50.05 | 57.87 | |
| Hypertension (%) | | | | 0.0006 |
| No | 71.62 | 64.71 | 58.72 | |
| Yes | 28.38 | 35.29 | 41.28 | |
| Diabetes (%) | | | | 0.0098 |
| No | 91.77 | 89.53 | 85.48 | |
| Yes | 8.23 | 10.47 | 14.52 | |
| CVD (%) | | | | 0.0001 |
| No | 93.06 | 89.83 | 85.26 | |
| Yes | 6.94 | 10.17 | 14.74 | |
| Other CRD (%) | | | | 0.2755 |
| No | 81.59 | 76.99 | 77.91 | |
| Yes | 18.41 | 23.01 | 22.09 | |
| Cancer (%) | | | | 0.3526 |
| No | 89.68 | 90.17 | 87.48 | |
| Yes | 10.32 | 9.83 | 12.52 | |
| Hay fever (%) | | | | 0.2535 |
| No | 86.61 | 90.53 | 88.52 | |
| Yes | 13.39 | 9.47 | 11.48 | |
| Status (%) | | | | 0.0022 |
| Alive | 93.43 | 92.48 | 87.81 | |
| Death | 6.57 | 7.52 | 12.19 | |
| SII (1000 cells/uL) | 464.00 (340.07,642.53) | 494.67 (362.14,685.46) | 538.09 (376.47,757.31) | 0.0005 |
| SIRI (1000 cells/uL) | 0.76 (0.53,1.00) | 1.05 (0.75,1.40) | 1.40 (1.00,1.92) | 0.0001 |
| Cholesterol (mmol/l) | 5.21 ± 0.06 | 4.94 ± 0.05 | 4.90 ± 0.06 | 0.0033 |
| Triglyceride (mmol/l) | 1.05 (0.74,1.49) | 1.28 (0.88,1.81) | 1.86 (1.15,2.91) | 0.0001 |

Note: Median and interquartile range (IQR) for continuous variables with non-normal distributions; mean ± standard error (SE) for continuous variables with normal distributions. Proportions were employed to describe categorical variables. SII: systemic immune inflammation index; SIRI: system inflammation response index; MHR: monocyte-high-density lipoprotein cholesterol ratio

Both internationally and domestically, considerable research has focused on the effects of HDL-C on blood lipid metabolism, as well as its contribution to anti-infection, anti-inflammatory, and antioxidant mechanisms. Previous studies have shown that serum HDL-C levels are associated with the prognosis of COPD, coronavirus disease 2019 and other respiratory diseases [28, 29]. Alterations in HDL-C levels have also been observed

**Table 2** Association between MHR and mortality in asthmatics

| | Model I | Model II | Model III |
|---|---|---|---|
| | **HR (95% CI) *P* value** | **HR (95% CI) *P* value** | **HR (95% CI) *P* value** |
| **MHR** | 2.64 (1.71, 4.07) 0.0001 | 2.10 (1.41, 3.11) 0.0002 | 1.93 (1.20, 3.11) 0.0068 |
| **MHR tertile groups** | | | |
| T1 (0.05–0.32) | Reference | Reference | Reference |
| T2 (0.32–0.48) | 1.09 (0.79, 1.51) 0.6046 | 1.16 (0.83, 1.61) 0.3756 | 1.06 (0.74, 1.50) 0.7611 |
| T3 (0.48–3.62) | 1.54 (1.14, 2.09) 0.0054 | 1.51 (1.10, 2.06) 0.0101 | 1.29 (0.88, 1.87) 0.1916 |
| ***P* for trend** | 0.0040 | 0.0087 | 0.1757 |

Note: Model I adjusted for none. Model II adjusted for age, race, and sex. Model III adjusted for all covariates

**Table 3** Threshold effect analysis of MHR and mortality in asthmatics

| | **HR (95% CI) *P* value** |
|---|---|
| **Mode 1** | |
| Linear effect | 1.93 (1.20, 3.11) 0.0068 |
| **Model 2** | |
| Inflection point (K) | 0.29 |
| < K | 0.07 (0.00, 1.82) 0.1081 |
| > K | 2.14 (1.35, 3.40) 0.0013 |
| ***P* for log likelihood ratio** | 0.0540 |

Note: Model 1 and 2 all adjusted all covariates

in various allergic diseases, including allergic rhinitis, atopic dermatitis, urticaria, and angioedema [30]. Evidence suggests that the composition and function of HDLs are altered in allergic diseases. One study found that patients with allergic rhinitis had lower levels of HDL apolipoprotein A-IV, an anti-inflammatory protein that inhibits eosinophil activity [31]. Preliminary studies have demonstrated that HDL's anti-inflammatory properties along with its ability to modulate the expression of adhesion factors across various tissues may play a protective role against asthma [32, 33]. Although several clinical investigations have explored the link between blood lipid levels and asthma incidence, the outcomes have varied. Some studies have found a direct relationship, others have noted no significant link, and a few have identified a negative relationship between HDL-C level

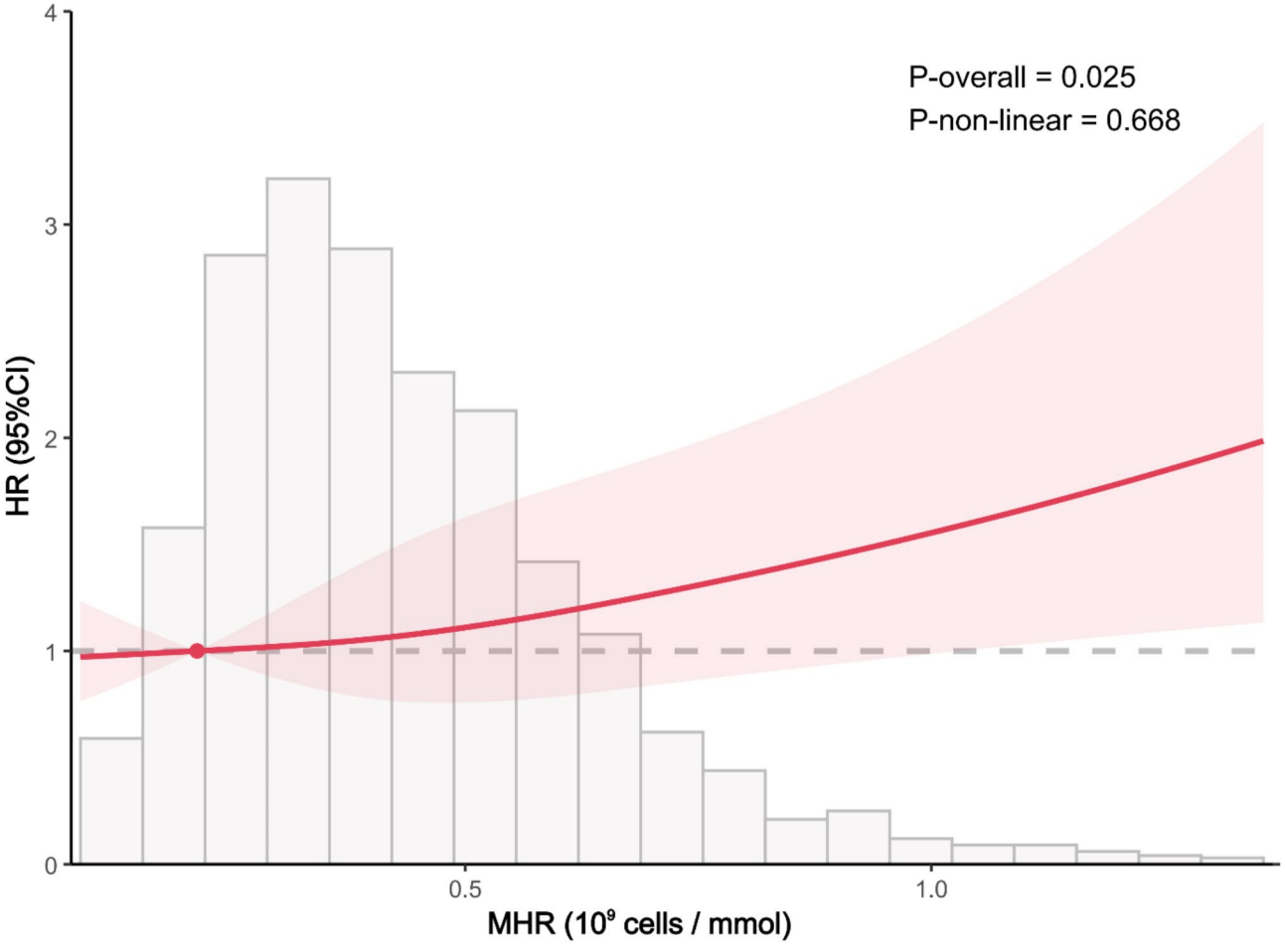


**Fig. 2** Dose-response correlation between MHR and mortality in asthmatics

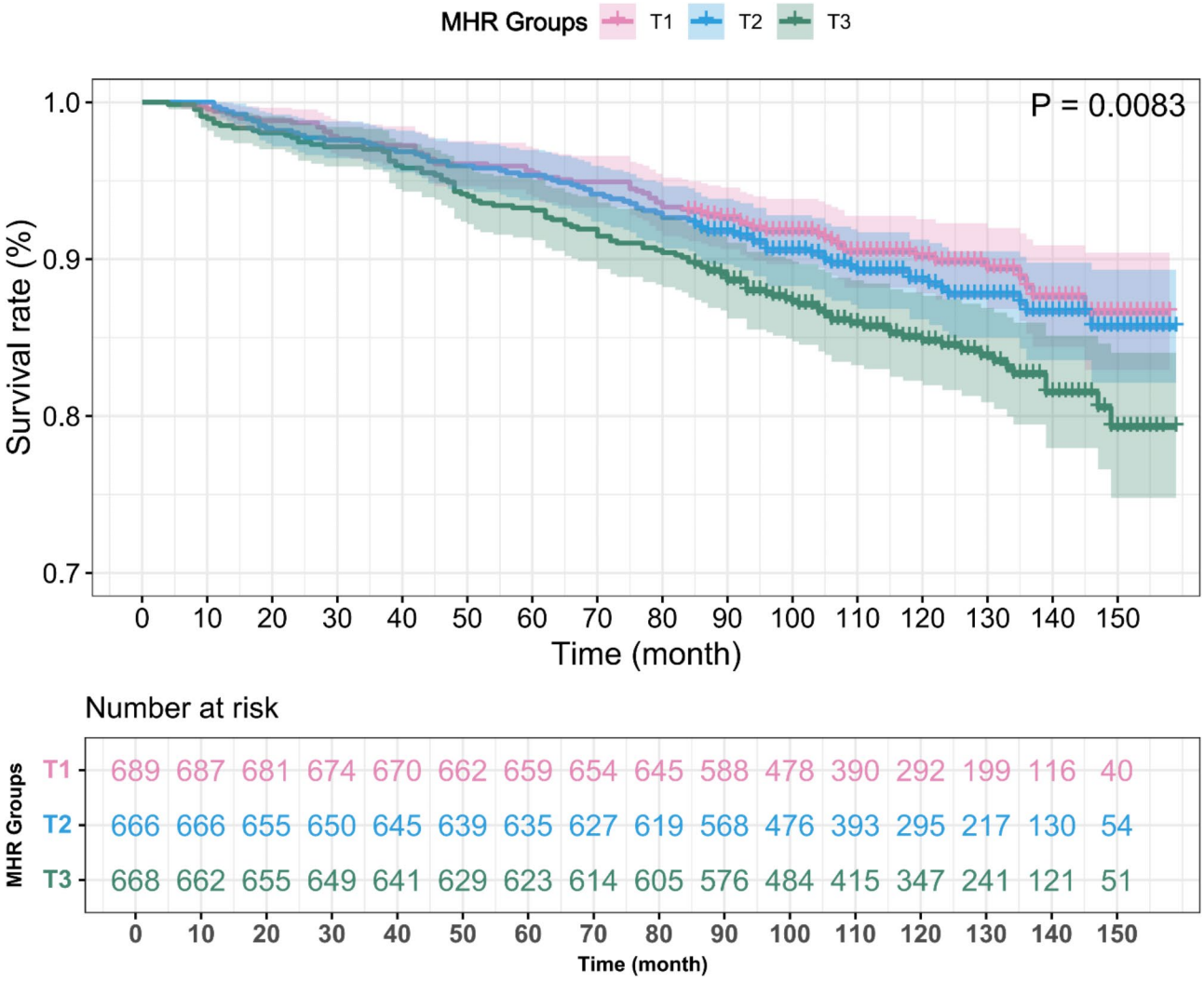


**Fig. 3** Kaplan-Meier analysis of survival rate by groups of MHR in asthmatics

and the risk of developing asthma [34–36]. Analyzing data from 10 cohort studies, a meta-analysis reported a remarkable negative association between serum HDL-C levels and asthma occurrence among adults and children alike [37]. Additionally, a Mendelian randomization study highlighted that lower levels of HDL-C were associated with an increased incidence of asthma [38]. Contrasting findings were presented by a comprehensive cross-sectional analysis using data from the UK Biobank, which found a positive correlation between HDL-C levels and asthma prevalence [39]. Research conducted within a US asthma cohort indicated no discernible independent link between HDL-C levels and asthma mortality [40]. Recent studies have also introduced novel hematological markers linked to HDL-C level, such as the neutrophil-to-HDL-C ratio and NHHR, which have been proposed as novel indicators of inflammation. A study by Ying et al. investigated the relationship between the NHHR and asthma prevalence among adults in the United States and found a significant inverse relationship. In addition, another study observed that this relationship may be influenced by sex [41].

In addition, several complex interactions between monocytes and HDL-C can influence the immune and inflammatory responses. HDL-C plays a crucial role in lipid metabolism and modulates the immune response through its direct effects on immune cells [42]. It also plays a crucial role in moderating the pro-oxidative and pro-inflammatory activities of monocytes, primarily by suppressing monocyte migration, inflammatory factor release, low-density lipoprotein cholesterol oxidation, and facilitating cholesterol efflux from these cells [42, 43]. It has been further corroborated by existing literature that HDL-C effectively reduces the proliferation and differentiation of monocyte progenitors [44]. Given the potent anti-inflammatory properties of HDL-C and the inflammatory nature of monocytes, an increasing volume of research supports the use of the MHR as a novel and

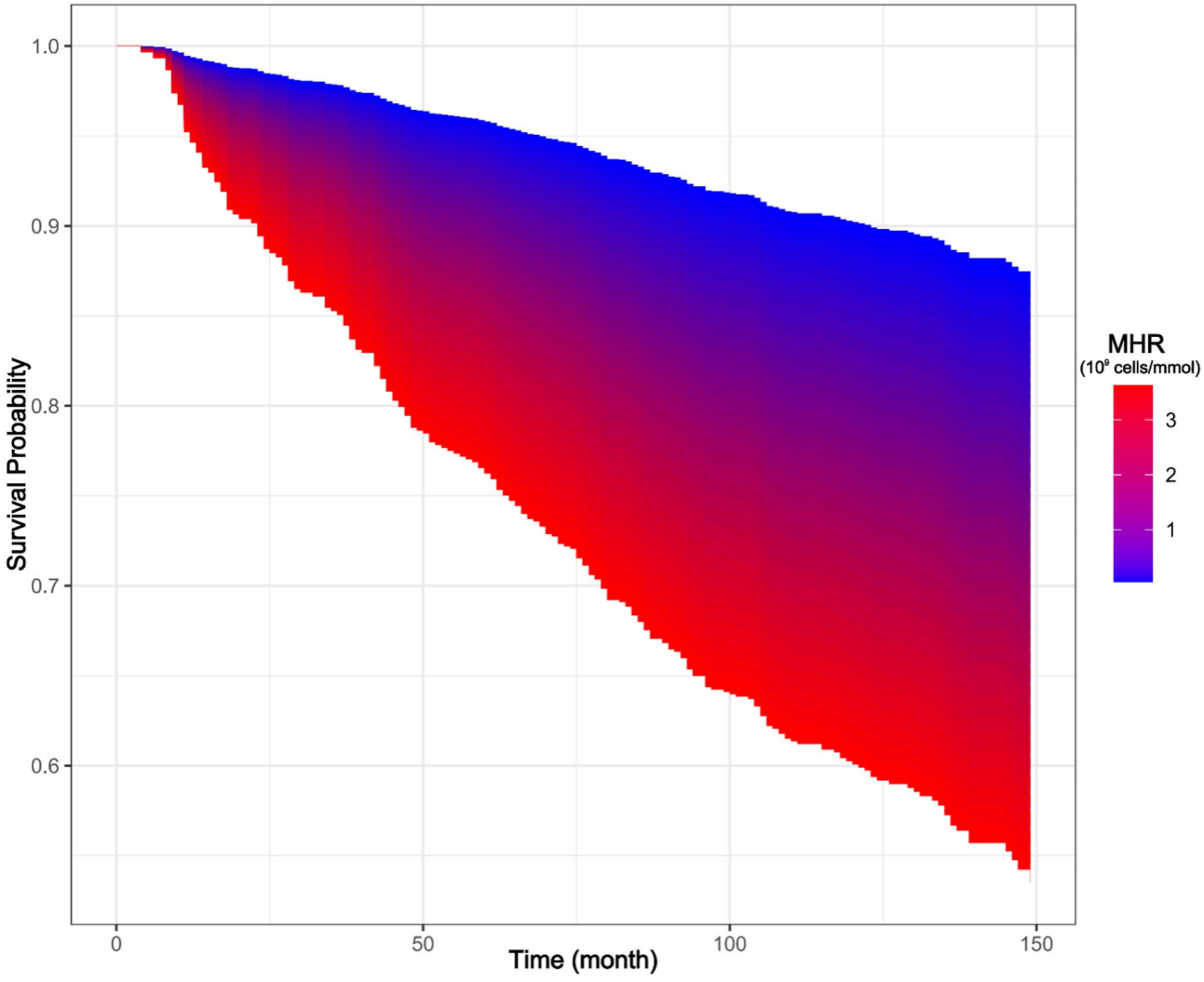


**Fig. 4** Survival area plot displayed estimates of the impact of MHR on the death risk during the follow-up period, based on Model III

comprehensive marker of both lipid metabolism and systemic inflammation. Numerous studies have established links between the MHR and a series of health conditions, involving gallstones, chronic kidney disease, post-stroke depression, and coronary heart disease [17, 45–47].

## Strengths and limitations of the study

The MHR serves as a novel composite predictor, offering superior predictive value for clinical outcomes compared with the monocyte count or HDL-C level alone. It is a well-established index and can be obtained through routine blood tests, making it a cost-effective alternative to expensive genomic or imaging tests. This investigation revealed a clear positive relationship between the MHR and a heightened risk of asthma-related mortality, underscoring its potential as a practical tool for identifying high-risk patients with asthma. This may enable early targeted interventions to improve patient management and reduce mortality rates. Unlike traditional markers, the MHR provides unique insights into the inflammatory status of patients with asthma, offering significant value in clinical practice. The integration of MHR into routine assessments can help personalize treatment plans and enhance outcomes. Although this study provides compelling evidence, further prospective cohort studies are needed to validate these findings and define MHR-based risk stratification thresholds for clinical decision-making.

However, certain limitations of the study need to be acknowledged. First, the asthma population was determined using standard medical questionnaires instead of bronchial provocation or relaxation tests, which may have potentially led to under- or overdiagnosis of asthma. In addition, we could not obtain information on asthma subtypes, severity, or medication use during follow-up. Furthermore, the survey did not incorporate information regarding additional potential allergic diseases because of database constraints. Finally, although some unknown

factors were considered, the effects of other unknown factors could not be ruled out.

## Conclusion

This longitudinal investigation indicated that an increased MHR was associated with elevated mortality in individuals with asthma. Thus, the MHR can be used as an independent biomarker to predict the prognosis of patients with asthma.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02484-y.

Supplementary Material 1

**Acknowledgements**
We appreciate the editage reviewing and editing our manuscript's language.

**Author contributions**
Conceptualization: QZ, CFW, JW, JX. Data collection: QZ, CFW. Statistical analysis: JW, RJZ. Original draft: QZ, RJZ, JX. Review & editing: JW, CFW. Project administration: CFW. QZ, JX, and RJZ made equal contributions, sharing the first author.

**Funding**
Qianxinan Prefecture Medical Science Research Joint Project (2024-32).

**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval**
The Research Ethics Review Board of the NCHS has approved all NHANES research protocols (Protocol #2011-17, Protocol #2018-01).

**Competing interests**
The authors declare no competing interests.

Received: 1 January 2025 / Accepted: 12 February 2025
Published online: 21 February 2025

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