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# Accelerated biological aging mediates the association between inflammatory markers with *Helicobacter pylori* infection and mortality

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## Abstract

**Background** The aim of this study was to explore the systemic inflammation response in relation to mortality in *Helicobacter pylori* (*H. pylori*) infection, and whether this relationship was mediated by accelerated biological aging.

**Methods** This cross-sectional study encompassed U.S. participants from National Health and Nutrition Examination Survey (NHANES) in 1999–2000. Kaplan-Meier survival curve, Cox regression analysis, K-means clustering, mediation analysis and restricted cubic spline (RCS) were used to explore the relationships between inflammatory markers, biological aging, *H. pylori* infection and all-cause mortality.

**Results** A total of 3509 U.S. participants enrolled form NHANES 1999–2000. Compared with *H. pylori* seronegative participants, *H. pylori* seropositive participants had significantly higher all-cause mortality ($P < 0.001$). Among these *H. pylori* seropositive participants, both phenotypic age acceleration (PhenoAgeAccel) and all-cause mortality were positively associated with the increased levels of inflammation ($P < 0.001$). A significant indirect effect of inflammatory markers (neutrophil count and systemic inflammatory response index (SIRI)) with *H. pylori* infection on all-cause mortality through PhenoageAccel was found, and the proportions mediated were 50.0% and 49.1%, respectively.

**Conclusion** The elevation of blood inflammatory markers is positively associated with an increased risk of all-cause mortality in *H. pylori* infection among U.S. population, and accelerated biological aging might be one of its biological mechanisms.

**Keywords** Accelerated biological aging, Inflammatory markers, *Helicobacter pylori* infection, All-cause mortality, Mediating effect

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## Introduction

*Helicobacter pylori* (*H. pylori*) is a common gram-negative bacterium that infects and colonizes the human stomach [1]. The global prevalence of *H. pylori* infection was estimated to be 43.9% during the 2015–2022 period [2, 3]. Due to the development of chronic inflammation of gastric mucosa, *H. pylori* infection is strongly associated with the chronic gastritis, peptic ulcers, gastric adenocarcinoma and mucosa associated lymphoid tissue (MALT) lymphoma [4, 5], and thus an increased risk of death. Moreover, *H. pylori* infection is believed to be associated with various extragastric diseases including neurological, metabolic, allergic and cardiovascular diseases and so on [6, 7].

Inflammation is closely related to *H. pylori* infection. Infection with *H. pylori* strains that expresses the CagA can induce a local robust inflammatory response and increase the risk for the development of gastric adenocarcinoma [8, 9]. *H. pylori*-associated gastritis includes many common blood inflammatory markers such as neutrophils, lymphocytes, monocytes and white blood cell (WBC) [10–12]. In addition, it was reported that the neutrophil/lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) might also be associated with *H. pylori* infection [11]. However, for other new inflammatory markers, including neutrophil-albumin ratio (NAR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI), there is a lack of evidence of the relationships between them and *H. pylori* infection. Furthermore, previous studies have shown that the elevation of these inflammatory markers are positively associated with an increased risk of all-cause mortality in extragastric diseases, such as cardiovascular, thoracic and urological diseases [13–15]. However, whether blood inflammation index affecting mortality in *H. pylori* infection patients remains unclear.

Aging is a complex biological process associated with disease risk and subsequent death [16]. At present, previous studies have demonstrated a significant relationship between chronic low-level inflammation and biological aging [17, 18], which is considered to be associated with oxidative stress, telomere attrition and autophagy and so on [19]. Moreover, accelerated biological aging is different from normal aging that it focuses on measuring the pace of aging and can lead to an increased risk of mortality [20]. Based on the combination of various clinical biomarkers, phenotypic age acceleration (PhenoAgeAccel) is a measurement to calculate biological age that represents the manifestations of multiple aging features at the cellular and intracellular levels [21]. Currently, there is a lack of relevant studies exploring the mediating role of accelerated biological aging in the association between systemic inflammation response with *H. pylori* infection and mortality.

Therefore, the present study aimed to investigate the cross-sectional correlation between blood inflammatory markers with *H. pylori* infection and mortality based on the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000. Then, we employed whether such relationship was mediated by accelerated biological aging, hoping to provide significant evidence on mechanism for inflammatory markers with *H. pylori* infection to mortality.

## Materials and methods

### Study design and population

NHANES is a public cross-sectional survey conducted by the National Center for Health Statistics (NCHS) to obtain nationally representative samples of the civilian nonhospitalized U.S. population (http://www.cdc.gov/nchs/nhanes/) [22]. The survey data included demographic, dietary, examination, laboratory and questionnaire information. The research protocols and procedures were approved by the NCHS Research Ethics Review Board, and written informed consent was obtained from all participants.

U.S. participants for this research were selected from NHANES 1999–2000, as *H. pylori* serology infection status was only measured during this cycle. The *H. pylori* serology data is recorded in Codename LBXHP1. A total of 9965 participants were included in NHANES 1999–2000 cycle. Then, 7493 participants *H. pylori* serology data were enrolled, and after further exclusion screening, 3509 participants were finally included for analysis, and further categorized into "*H. pylori* seronegative" group and "*H. pylori* seropositive" group based on the enzyme-linked immunoassay (ELISA) test finding of *H. pylori* immunoglobulin G (IgG) antibody detection (Fig. 1).

### *Helicobacter pylori* infection status

For U.S. participants form NHANES, *H. pylori* IgG ELISA was used to evaluate *H. pylori* IgG antibodies of the serum samples by Wampole Laboratories (Cranbury, NJ). According to standard ELISA cut-offs, participants were divided into *H. pylori* seropositive (optical density (OD) value ≥ 1.1) and *H. pylori* seronegative (OD value < 0.9). Participants with equivocal values (0.9–1.1) were excluded from this study to avoid misleading statistical outcomes [23].

### Inflammatory markers

We employed WBC count, neutrophil count, lymphocyte count, NLR, PLR, NAR, SII and SIRI as inflammatory markers in this study. WBC, neutrophil and lymphocyte count in 1000 cells/μL from peripheral blood count were obtained directly from the NHANES, while other inflammatory factors were obtained indirectly by calculation as following: NLR was neutrophil to lymphocyte ratio; PLR

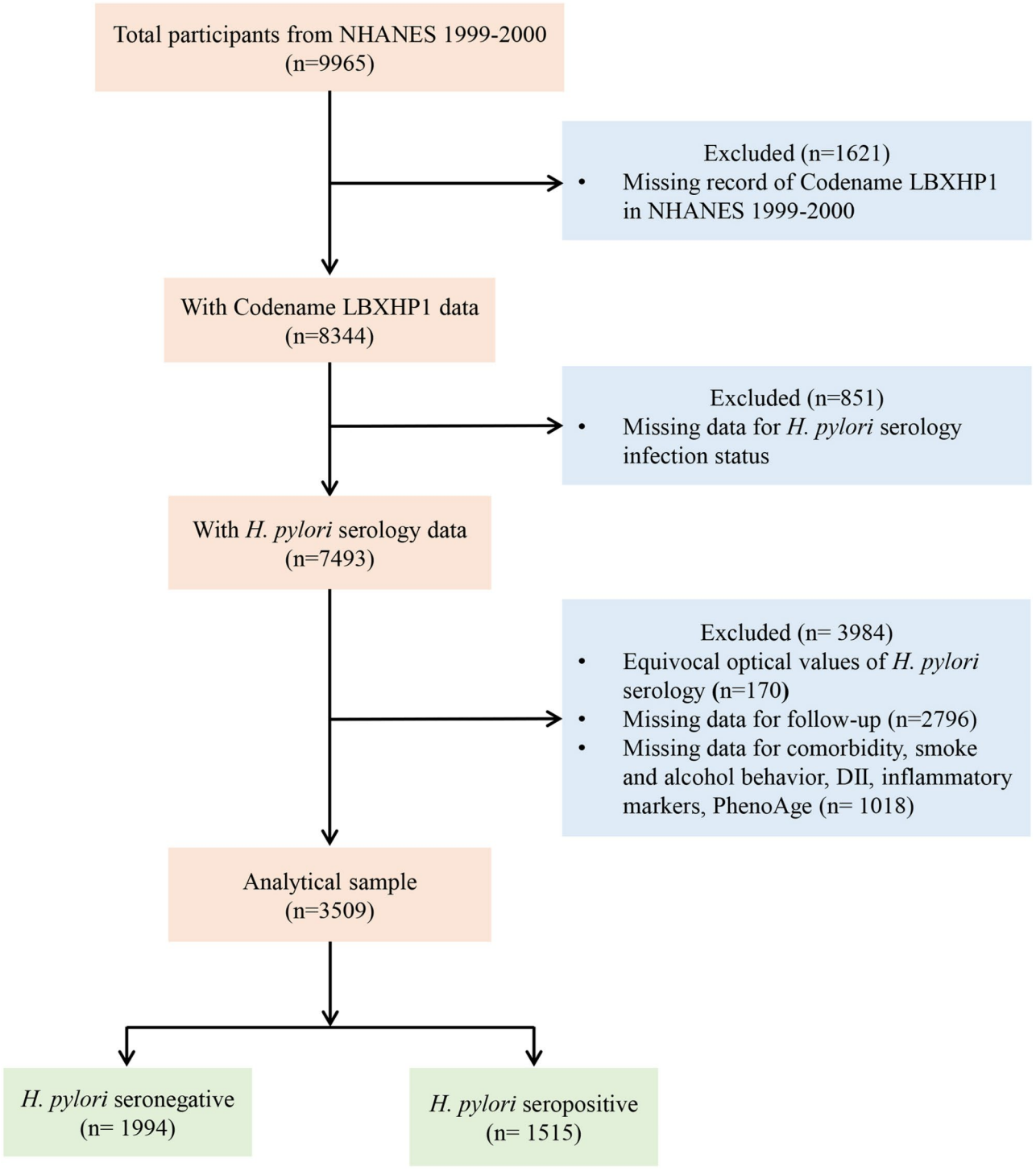



**Fig. 1** A flowchart of U.S. participants included in this study

was platelet to lymphocyte ratio; NAR was neutrophil to albumin ratio; SII was calculated as platelet count * neutrophil count/lymphocyte count; SIRI was calculated as neutrophil count * monocyte count/lymphocyte count [24].

### Phenotypic aging

Phenotypic age (PhenoAge) was calculated by using chronological age and nine clinical biomarkers [21, 25], including albumin, creatinine, glucose, C-reactive protein (CRP), lymphocyte percent, mean cell volume (MCV), red blood cell distribution width, alkaline phosphatase,

and WBC count. The equation for calculating PhenoAge was as follows [21]:

$$PhenoAge = 141.50 + \frac{\ln\left[-0.00553 \times \ln\left(1 - M\right)\right]}{0.09165}$$

Where

$$M = 1 - exp\left(\frac{-1.51714 \times exp\left(xb\right)}{0.0076927}\right)$$

$$\begin{aligned} xb = &-19.907 - 0.0336 \times Albumin + 0.0095 \times Creayinine \\ &+0.1953 \times Glucose + 0.0954 \times ln\left(CRP\right) \\ &-0.0120 \times LymphocytePercent + 0.0268 \times MCV \\ &+0.3306 \times Red\ blood\ cell\ distribution\ width \\ &+0.00188 \times Alkaline\ phosphatase + 0.0554 \\ &\times WBC\ count + 0.0804 \times Chronological\ age \end{aligned}$$

PhenoAgeAccel was employed to avoid the confounding effects of chronological age, calculated as a residual from a linear regression of PhenoAge against chronological age [21].

### Mortality

The outcome of this study for U.S. participants form NHANES was all-cause mortality, including all causes of death. Information on all-cause mortality was determined by linkage to the recorded on the NHANES-linked National Death Index (NDI) public access records, until December 31, 2019 [26]. The median (interquartile range (IQR)) duration of follow-up for *H. pylori* positive participants was 235 (184–243) months, while 236 (229–242) months for *H. pylori* negative participants.

### Covariate

Previous studies have shown many factors associated with *H. pylori* infection [27–29]. In this study, chronological age, sex, race, education, body mass index (BMI), smoking and drinking behavior, comorbidity and dietary inflammation index (DII) were selected as covariates. Among them, chronological age, BMI and DII were applied as continuous variables; sex, race, education, smoking and drinking behavior, and comorbidity were applied as categorical variables. DII was employed to evaluate the potential inflammatory effects from dietary intake. Previous study has indicated that DII was positively associated with the risk of *H. pylori* infection and mortality [30]. In this study, DII was calculated by 26 food components, including alcohol, vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin E, β-carotene, caffeine, carbohydrate, cholesterol, total fat, fiber, folic acid, iron, magnesium, zinc, selenium, monounsaturated fatty acids, niacin, n-3 fatty acids, n-6 fatty acids, protein, polyunsaturated fatty acids, riboflavin, saturated fat, and thiamin [30]. Food components with anti-inflammatory properties scored negative, while pro-inflammatory substances scored positive [31]. Then, the DII score of every participant was calculated by summing up the scores obtained from these 26 food components. Furthermore, the comorbidity of participant was comprised of hypertension, diabetes and renal failure. More detailed information on covariates is publicly available at http://www.cdc.gov/nchs/nhanes/.

### Statistical analyses

For continuous variables, normally distributed variables were presented as mean ± standard deviation (SD), and compared using Student's t test, while non-normally distributed variables were presented as median and IQR in parentheses, and analyzed using Mann–Whitney U test. Categorical variables were presented as frequencies and percentages, and were evaluated using the Chi-squared or Fisher's exact test where appropriate.

The Kaplan-Meier survival curve analysis and log-rank test were used to assess the relationship between *H. pylori* serology infection status and all-cause mortality. Cox regression analysis was performed to explore the association between inflammatory markers and biological aging, and allcause mortality respectively. We employed K-means clustering algorithm to group *H. pylori* seropositive participants into three groups by inflammatory markers. An available R package named "mediation" was used to perform the mediation analyses of biological aging in the association between inflammatory markers with *H. pylori* infection and mortality [32]. Furthermore, restricted cubic spline (RCS) was used to assess the potential non-linearity association between biological aging and the risks of allcause mortality in patients with different *H. pylori* infection and inflammation status. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the R software version 4.1.1 (www.rproject.org).

## Result

### Characteristics of the study participants

A total of 3509 U.S. participants were finally included in the analyses, of which 1994 (56.83%) participants were *H. pylori* seronegative and 1515 (43.17%) were *H. pylori* seropositive (Fig. 1). Among the total participants, the average chronological age was 49.72 ± 18.49 years old, and 47.34% were male. In these two groups, chronological age, race, educational level, alcohol behavior, hypertension status, diabetes status, renal failure status and DII were significantly different ($P < 0.05$). For inflammatory markers, compared with *H. pylori* seronegative participants, participants with *H. pylori* seropositive had higher lymphocyte count and lower neutrophil count, NLR, PLR, NAR, SII and SIRI ($P < 0.05$). Moreover, *H. pylori* seropositive participants had higher PhenoAge and

PhenoageAccel ($P<0.05$). The baseline characteristics of participants are presented in Table 1.

### Associations between *H. pylori* serology infection status, inflammatory markers and biological aging, and all-cause mortality, respectively

Among the total participants, 1090 (31.06%) participants experienced death. The Kaplan-Meier survival curve analysis demonstrated that *H. pylori* seropositive infection status was associated with higher all-cause mortality ($P<0.001$) (Fig. 2). Cox regression analysis showed that inflammatory markers including neutrophil count ($P=0.007$), NLR ($P<0.001$), NAR ($P<0.001$), SII ($P<0.001$) and SIRI ($P<0.001$) were positively associated with higher all-cause mortality (Table 2). Moreover, biological aging including PhenoAge ($P<0.001$) and PhenoageAccel ($P<0.001$) were also both positively associated with higher all-cause mortality (Table 2).

Then, we used K-means clustering algorithm to group *H. pylori* seropositive participants into three groups by inflammatory markers. According to the different degree of inflammation, we defined Cluster 1 as the "low-level inflammation group", Cluster 2 as the "moderate-level inflammation group", and Cluster 3 as the "high-level inflammation group". Compared with *H. pylori* seronegative participants, *H. pylori* seropositive participants with different levels of inflammation all had significantly higher all-cause mortality (Fig. 3B) ($P<0.001$). In *H. pylori* seropositive participants, both PhenoageAccel (Fig. 3A) and all-cause mortality (Fig. 3B) showed positive associations with elevated inflammation levels ($P<0.001$).

**Table 1** Baseline characteristics of participants stratified by H. Pylori infection status

| Variables | All subjects (*N* = 3509) | H. pylori seronegative (*N* = 1994) | H. pylori seropositive (*N* = 1515) | *p* value |
|---|---|---|---|---|
| Sex (n [%]) | | | | 0.175 |
| Male | 1661 (47.34) | 924 (46.34) | 737 (48.65) | |
| Female | 1848 (52.66) | 1070 (53.66) | 778 (51.35) | |
| Age (years), Mean ± SD | 49.72 ± 18.49 | 47.19 ± 18.70 | 53.06 ± 17.66 | < 0.001* |
| Race (n [%]) | | | | < 0.001* |
| Mexican American | 920 (26.22) | 313 (15.70) | 607 (40.07) | |
| Other Hispanic | 222 (6.33) | 89 (4.46) | 133 (8.78) | |
| Non-Hispanic White | 1666 (47.48) | 1274 (63.89) | 392 (25.87) | |
| Non-Hispanic Black | 600 (17.10) | 261 (13.09) | 339 (22.38) | |
| Other Race | 101 (2.88) | 57 (2.86) | 44 (2.90) | |
| Education (n [%]) | | | | < 0.001* |
| Less than high school | 1283 (36.56) | 439 (22.02) | 844 (55.71) | |
| High school diploma | 796 (22.68) | 511 (25.63) | 285 (18.81) | |
| More than high school | 1430 (40.75) | 1044 (52.36) | 386 (25.48) | |
| BMI (kg/m$^2$), Mean ± SD | 28.42 ± 6.16 | 28.27 ± 6.23 | 28.63 ± 6.06 | 0.084 |
| Smoking behavior (n [%]) | 1683 (47.96) | 928 (46.54) | 755 (49.83) | 0.053 |
| Alcohol behavior (n [%]) | 2344 (66.80) | 1375 (68.96) | 969 (63.96) | 0.002* |
| Comorbidity (n [%]) | | | | |
| Hypertension | 1054 (30.04) | 545 (27.33) | 509 (33.60) | < 0.001* |
| Diabetes mellitus | 323 (9.20) | 137 (6.87) | 186 (12.28) | < 0.001* |
| Renal failure | 103 (2.94) | 48 (2.41) | 55 (3.63) | 0.033* |
| DII, Mean ± SD | 1.08 ± 2.38 | 0.83 ± 2.40 | 1.41 ± 2.30 | < 0.001* |
| Inflammatory markers, Mean ± SD | | | | |
| WBC count | 7.31 ± 2.14 | 7.35 ± 2.19 | 7.27 ± 2.08 | 0.256 |
| Neutrophil count | 4.41 ± 1.76 | 4.51 ± 1.82 | 4.26 ± 1.66 | < 0.001* |
| Lymphocyte count | 2.10 ± 0.75 | 2.02 ± 0.74 | 2.19 ± 0.74 | < 0.001* |
| NLR | 2.31 ± 1.23 | 2.45 ± 1.33 | 2.12 ± 1.05 | < 0.001* |
| PLR | 137.31 ± 57.25 | 141.49 ± 57.15 | 131.81 ± 56.95 | < 0.001* |
| NAR | 0.10 ± 0.04 | 0.10 ± 0.05 | 0.10 ± 0.04 | < 0.001* |
| SII | 604.57 ± 372.49 | 636.72 ± 395.41 | 562.26 ± 335.44 | < 0.001* |
| SIRI | 1.35 ± 0.94 | 1.45 ± 1.02 | 1.23 ± 0.81 | < 0.001* |
| PhenoAge (years), Mean ± SD | 42.94 ± 20.62 | 39.95 ± 20.54 | 46.88 ± 20.07 | < 0.001* |
| PhenoageAccel (years), Mean ± SD | -0.28 ± 6.98 | -0.61 ± 6.47 | 0.17 ± 7.58 | 0.001* |

SD, standard deviation; BMI, body mass index; DII, dietary inflammatory index; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NAR, neutrophil-to-albumin ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; PhenoAge, phenotypic age; PhenoAgeAccel, phenotypic age acceleration. **P*-value < 0.05

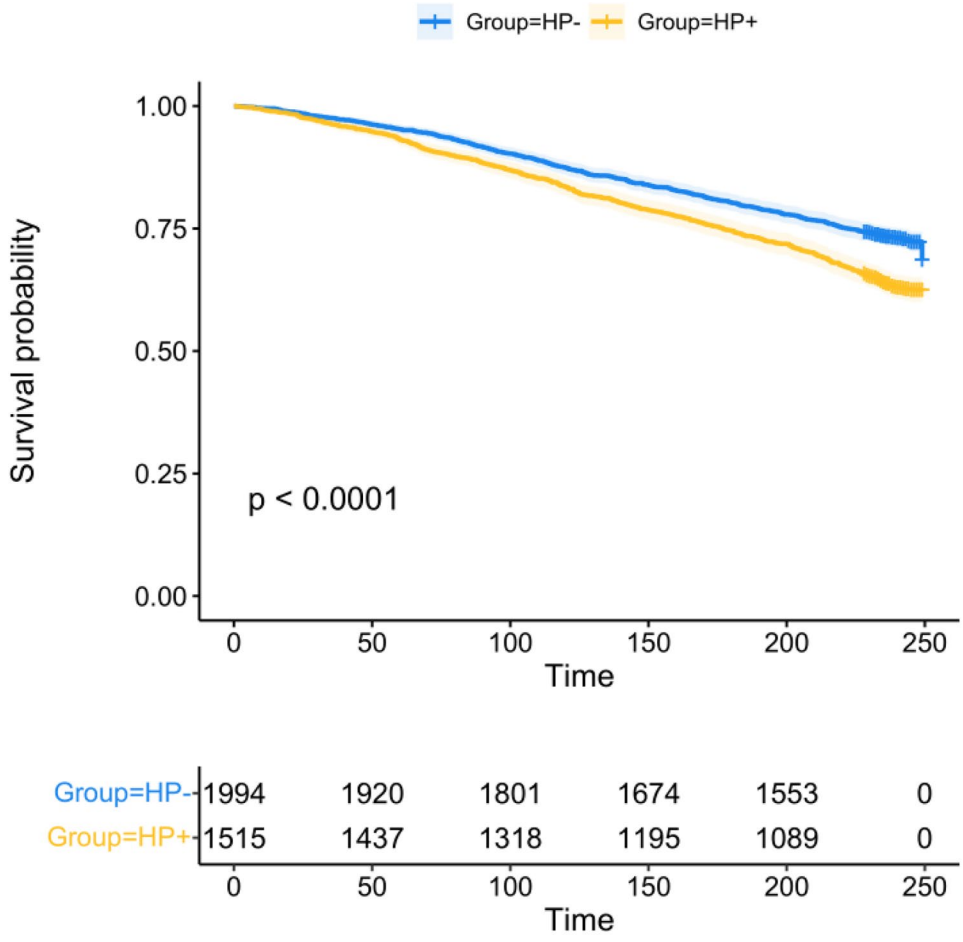



**Fig. 2** Kaplan–Meier survival estimates for allcause mortality in *H.pylori* seropositive and seronegative participants

**Table 2** Associations between inflammatory markers and biological aging, and allcause mortality respectively

| Variables | HR | 95%CI | *p* value |
|---|---|---|---|
| Inflammatory markers | | | |
| Neutrophil count | 1.07 | 1.02–1.12 | 0.007* |
| NLR | 1.20 | 1.12–1.29 | < 0.001* |
| NAR | 27.14 | 4.34-169.74 | < 0.001* |
| SII | 1.00 | 1.00–1.00 | < 0.001* |
| SIRI | 1.28 | 1.19–1.38 | < 0.001* |
| Biological aging | | | |
| PhenoAge | 1.07 | 1.06–1.07 | < 0.001* |
| PhenoageAccel | 1.05 | 1.04–1.06 | < 0.001* |

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; NAR, neutrophil-to-albumin ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; PhenoAge, phenotypic age; PhenoAgeAccel, phenotypic age acceleration. **P*-value < 0.05

### Mediating effect of accelerated biological aging on association between inflammatory markers with *H. pylori* infection and all-cause mortality

The mediation analyses of accelerated biological aging in the association between inflammatory markers with *H. pylori* infection and mortality are presented in Tables 3 and 4. We found a significant indirect effect of inflammatory markers (neutrophil count and SIRI) with *H. pylori* infection on all-cause mortality through PhenoageAccel (Fig. 4). The proportions mediated by PhenoageAccel for the neutrophil count-associated all-cause mortality were 50.0%, for the SIRI-associated all-cause mortality were 49.1%.

To further verify the relationship between the above factors, the association between biological aging and the risks of allcause mortality in patients with different *H. pylori* infection and inflammation status was assessed by RCS curve (Fig. 5). The RCS analysis revealed a significant positive correlation between biological aging and the risks of allcause mortality, and this association was stronger in *H. pylori* seropositive group than *H. pylori* seronegative group. In the meanwhile, for *H. pylori* seropositive group, the association between biological aging and the risk of mortality was strongest in the high-level inflammation group, followed by the moderate-level inflammation group, and weakest in the low-level inflammation group.

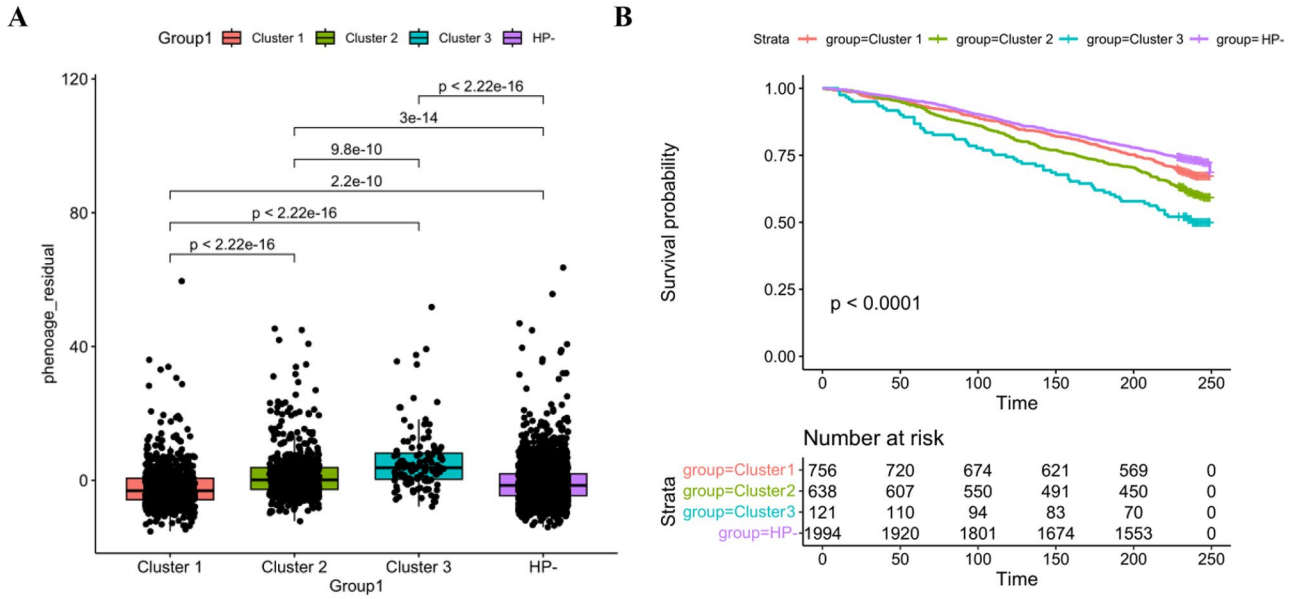



**Fig. 3** Comparison of PhenoageAccel (**A**) and all-cause mortality (**B**) in *H.pylori* seronegative participants and seropositive participants stratified by inflammatory markers. "Cluster 1" means "low-level inflammation group", "Cluster 2" means "moderate-level inflammation group", "Cluster 3" means "high-level inflammation group"

**Table 3** Mediation of accelerated biological aging for the association between inflammatory marker (neutrophil count) and all-cause mortality

| Effects of accelerated biological aging | Coefficients (95%CIs) | *p* value | Proportions mediated (%) |
|---|---|---|---|
| Indirect (ab) | 0.015 (0.012–0.018) | < 0.001* | 50.0 |
| Direct (c') | 0.014 (0.008–0.021) | < 0.001* | |
| Total (c) | 0.030 (0.023–0.036) | < 0.001* | |

CI, confidence interval; ab, indirect effect; c', direct effect; c, total effect. **P*-value < 0.05

**Table 4** Mediation of accelerated biological aging for the association between inflammatory marker (SIRI) and all-cause mortality

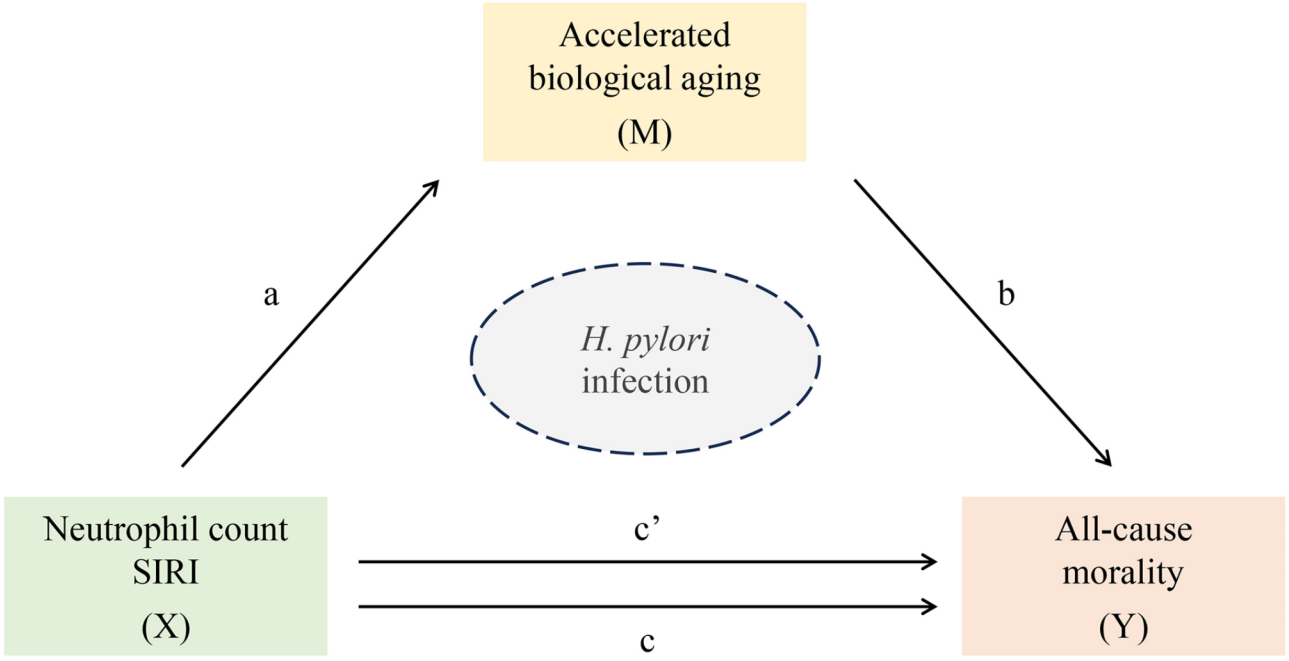
| Effects of accelerated biological aging | Coefficients (95%CIs) | *p* value | Proportions mediated (%) |
|---|---|---|---|
| Indirect (ab) | 0.026 (0.021–0.031) | < 0.001* | 49.1 |
| Direct (c') | 0.027 (0.014–0.039) | < 0.001* | |
| Total (c) | 0.053 (0.041–0.065) | < 0.001* | |

SIRI, systemic inflammatory response index; CI, confidence interval; ab, indirect effect; c', direct effect; c, total effect. **P*-value < 0.05

## Discussion

*H. pylori*, classified as a Group I carcinogen by the World Health Organization (WHO), is known to increase the risk of gastric cancer and all-cause mortality [33]. In our present study, there were two novel findings obtained based on the large sample of U.S. population from NHANES. First, the blood inflammatory markers were positively associated with higher all-cause mortality in *H. pylori* infection patients. Furthermore, accelerated biological aging was identified as a mediator for the positive association between inflammatory markers with *H. pylori* infection and all-cause mortality.

Compared with traditional inflammatory markers such as the WBC count, neutrophil count and lymphocyte count, NLR, PLR, NAR, SII and SIRI are novel composite inflammatory markers calculated from multiple cells counts according to the formula, which have been potentially related to various diseases of the elderly, including cardiovascular and cerebrovascular diseases [34–36]. At present, the specific correlation between various inflammatory markers and the persistent *H. pylori* infection has not been clarified. In 2013, Jafarzadeh et al. demonstrated the WBC count, neutrophil count and NLR were significantly higher among *H. pylori* positive patients compared with *H. pylori* negative patients [10]. However, Guclu et al. later reported that the NLR were significantly lower and lymphocytes were significantly higher among *H. pylori* positive patients [37]. In 2019, Melit et al. showed there were no significant differences in PLR and NLR between *H. pylori*-associated gastritis children and healthy controls [38]. Currently, there is a lack of study on the relationship between NAR, SII and SIRI with *H. pylori* infection, respectively. In our study, for U.S. participants form NHANES, compared with *H. pylori* seronegative participants, the neutrophil count, NLR, PLR, NAR, SII and SIRI were all significantly lower among *H. pylori* seropositive participants, and the lymphocyte




$$\text{Proportions mediated} = \frac{\text{Total effect (c)} - \text{Direct effect (c')}}{\text{Total effect (c)}} \times 100\%$$

**Fig. 4** The mediating role of accelerated biological aging for the association between inflammatory marker (neutrophil count and SIRI) and all-cause mortality. ab, indirect effect; c', direct effect; c, total effect

count were significantly higher among *H. pylori* seropositive patients, which is similar to the previous study [37].

Previous studies have shown that the inflammatory markers are strongly associated with an increased risk of all-cause mortality in various diseases. It has been reported that the inflammatory markers can predict the poor prognosis and all-cause mortality among patients with obstructive lung function, osteopenia and tuberculosis and so on [15, 39, 40]. However, this is the first study to explore the association between inflammatory markers and all-cause mortality among patients with *H. pylori* infection, and we demonstrated that the elevated inflammatory markers were positively associated with the all-cause mortality among patients with *H. pylori* infection.

Biological aging can reflect the aging degree of the individuals better than chronological age, and it has been demonstrated as a risk factor for the various diseases incidence and mortality including non-alcoholic fatty liver disease and cardiovascular disease [41, 42]. Telomere shortening is associated with cellular aging and decreased tissue renewal capacity in many organs and tissues [43]. Previous studies have indicated that telomere attrition is closely associated with *H. pylori* infection and its induced gastritis [44, 45]. Therefore, we explored the associated between the *H. pylori* infection and biological aging. Different from normal biological aging, PhenoageAccel focuses more on measuring the speed of aging by integrating clinical biomarkers that offering a broad perspective. Given its specificity for accelerated aging driven by inflammation, PhenoageAccel was selected as the more appropriate marker to assess the aging-mortality relationship in the context of *H. pylori* infection. Previous literature has shown that it is closely associated with an increased risk of stroke, circadian syndrome, and all-cause mortality [46, 47]. In our study, the PhenoAge and PhenoageAccel were both significantly older among *H. pylori* seropositive patients than seronegative participants. Furthermore, through mediation analysis, we found that accelerated biological aging has a mediating effect between blood inflammatory markers (neutrophil count and SIRI) and all-cause mortality in *H. pylori* infection individuals, which is important for further exploration of mechanism for inflammatory markers with *H. pylori* infection to mortality.

To our best knowledge, this is the first study to investigate the association between blood inflammatory markers

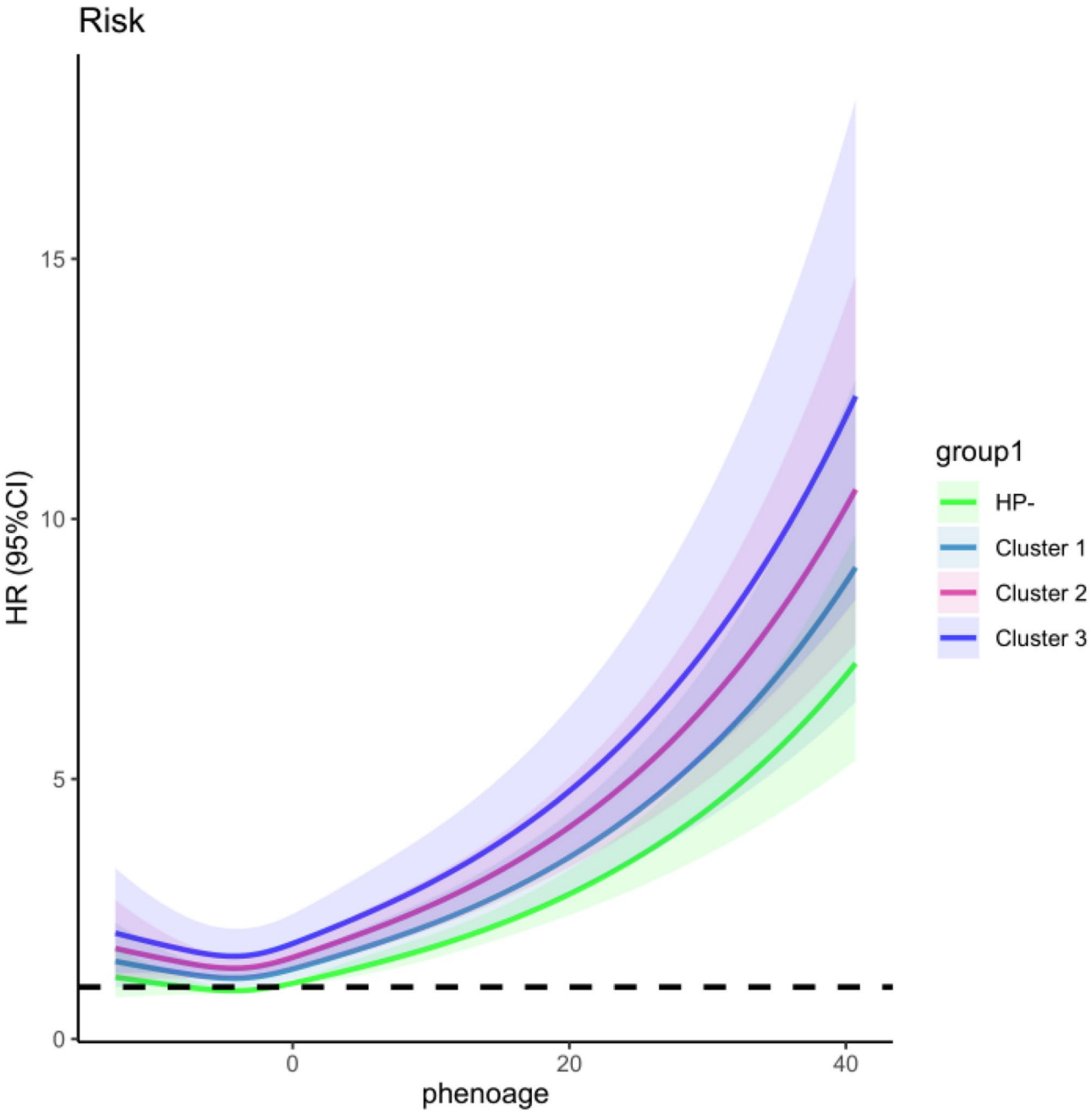



**Fig. 5** Restricted cubic spline (RCS) for the association between accelerated biological aging and the risks of allcause mortality in *H.pylori* seronegative participants and seropositive participants stratified by inflammatory markers. "Cluster 1" means "low-level inflammation group", "Cluster 2" means "moderate-level inflammation group", "Cluster 3" means "high-level inflammation group"

with *H. pylori* infection and mortality, and the mediating role of accelerated biological aging on such relationship, based on the large sample size of U.S. participants. However, our study has the following limitations. First, the data used in this study were limited to the NHANES 1999–2000 due to the *H. pylori* serological data was only available during these two years in NHAHES. Second, as NHANES database only provides serological data for *H. pylori* infection, we cannot differentiate if the infection is past or current for *H. pylori* seropositive participants. While serology is a widely used and reliable method for assessing *H. pylori* status in large epidemiological studies [30, 48], it does not capture infection activity, limiting our ability to assess the differential impact of chronic versus acute infections on biological aging. Future studies are encouraged to utilize more specific diagnostic tools, such as urea breath tests or histological examinations, and incorporate longitudinal data to better understand

the cumulative effects of chronic infection on aging and mortality. Finally, the U.S. participants included in our study were all from NHANES survey database and most of which were healthier than inpatient, which may not be generalizable to other countries and patients in hospital. Therefore, future researches should aim to validate these findings in more diverse populations, including individuals from different cultural and healthcare settings, as well as those with varying levels of health status, such as hospitalized or high-risk patients. Expanding the scope to include international cohorts and clinical populations would provide a more comprehensive understanding of the relationship between *H. pylori* infection, biological aging, and mortality.

## Conclusion

In summary, our study found that the elevation of blood inflammatory markers is positively associated with an increased risk of all-cause mortality in *H. pylori* infection among U.S. population. Meanwhile, mediation analysis revealed this relationship was statistically mediated by accelerated biological aging, indicating that accelerated biological aging could be one crucial mechanism whereby systemic inflammation response with *H. pylori* infection causes mortality. Large-scale studies are needed to confirm our findings and further explore the underlying mechanisms.

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**Author contributions**
JQ, HF and DL collected data, analyzed relevant information, and drafted the manuscript. QL, JX and YW contributed to statistical analysis and manuscript revision. SC and YX designed the study, critically revised the paper and approved the final submission. All authors contributed to the article and approved the submitted version.

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## Declarations

**Disclosures**
Jiayu Qiu, Hui Fang, Dingwei Liu, Qirui Lai, Jinliang Xie, Youhua Wang, Sihai Chen and Yong Xie have no conflicts of interest or financial ties to disclose.

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